Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 8629–8640

TETRAHEDRON

Synthesis and reactivity of lithium tri(quinolinyl)magnesates

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Received 9 April 2003; revised 22 May 2003; accepted 16 June 2003

Abstract—2-, 3- and 4-Bromoquinolines were converted to the corresponding lithium tri(quinolinyl)magnesates at −10°C when exposed to Bu_3MgLi in THF. The resulting organomagnesium derivatives were quenched with various electrophiles or involved in metal-catalyzed coupling reactions with heteroaryl halides to afford functionalized quinolines.

1. Introduction

Interest in azine (pyridine, quinoline…) and diazine products either for pharmaceuticals or as building blocks for various applications within materials science and supramolecular chemistry has led to extensive efforts devoted to a variety of synthetic methodologies.[1] Notably, the uses of organolithium,[1b–d] organoboron,[2] organotin,[2b,c,3] organozinc[2b,c,4] and organomagnesium[2b,c] compounds allow many functionalizations, either by trapping with electrophiles or cross-coupling reactions.

In the quinoline series, where the compounds are particularly prone to nucleophilic addition due to their low LUMO levels, the lithiation[1b,c] and halogen–lithium exchange[5] reactions used require low temperatures, which can be difficult to realize on an industrial scale. The uses of superbases by Caubère[6] or zincates by Kondo[7] could help to bias the reactions in favour of deprotonation, however, they are limited to the syntheses of 2- or 8-substituted quinolines.

An access to pyridinylmagnesium halides, through halogen–metal exchange of bromopyridines, was developed using isopropylmagnesium chloride in tetrahydrofuran (THF).[8] Nevertheless, when bromoquinolines were involved in the protocol, the corresponding quinolinylmagnesium halides were not obtained. Due to the lower LUMO levels of such substrates, the nucleophilic attack of the base to the quinoline ring was favoured over the exchange reaction. We had, therefore, to turn our attention to other magnesium species.

We recently accomplished the bromine–magnesium exchange of 2-, 3- and 4-bromoquinolines using lithium tributylmagnesate (Bu_3MgLi); the lithium tri(quinolinyl)-magnesates, thus obtained were either trapped with electrophiles[9] or involved in transition metal-catalyzed cross-couplings.[10]

Herein, the details of our investigations on the elaboration and the reactivity of such magnesium intermediates are recorded. In situ IR spectroscopy was used to monitor their formation and consumption.

2. Results and discussion

Since a magnesium ate complex (R_3MgLi) was first published in 1951,[11] several investigations on its structure have been reported.[12] However, synthetic applications of magnesate reagents remained seldom explored until very recently.[13] Oshima published in 2001 the first halogen–magnesium exchanges via organomagnesium ate complexes in the benzene, pyridine and thiophene series.[13i,l] The same year, the mono-exchange of dibromobenzenes and dibromoheteroarenes (pyridine and thiophene series) was developed by Iida and Mase using Bu_3MgLi.[13m]

Our initial experiments were conducted using Bu_3MgLi, prepared by mixing BuMgCl and BuLi in a 1:2 ratio.[13m] The formation of the magnesate was monitored using the in situ infrared spectroscopy. The spectra were recorded with a ReactIR™ 4000 fitted with an immersible DiComp ATR probe.[14] The experiment was conducted as follows: BuLi was added to BuMgCl at −75°C and the temperature was slowly allowed to reach −10°C. The absorbance associated with BuMgCl (1034, 1068 and 1494 cm^{-1}) rapidly decreased upon addition of BuLi, while the absorbance associated with Bu_2Mg (1467 cm^{-1}) increased[15] at low temperatures (between −75 and −40°C). Next, the disappearance of Bu_2Mg (1467 cm^{-1}) and the appearance

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Keywords: quinolines; ate complexes; in situ IR; cross-coupling.

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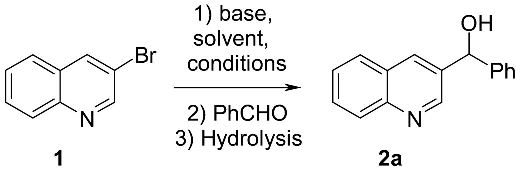
doi:10.1016/j.tet.2003.06.001



Scheme 1.

Table 1. Optimization of the bromine–magnesium exchange of **1**

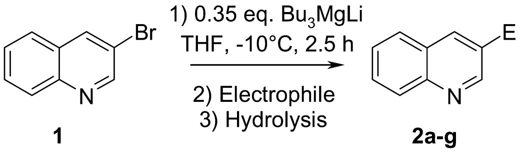
Entry	Base (equiv.)	Solvent	Conditions	Yield (%)
1	Bu_3MgLi (0.35)	Toluene	−10°C, 2.5 h	65
2	Bu_3MgLi (0.66)	Toluene	−10°C, 2.5 h	8
3	Bu_3MgLi (1.0)	Toluene	−10°C, 2.5 h	0
4	Bu_3MgLi (0.35)	Toluene	rt, 2.0 h	48
5	Bu_3MgLi (0.35)	Toluene	Reflux, 30 min	42
6	Bu_3MgLi (0.35)	THF	−10°C, 2.5 h	89
7	Bu_3MgLi (0.35)	MTBE	−10°C, 2.5 h	71
8	Bu_3MgLi (0.35)	Et_2O	−10°C, 2.5 h	56
9	Bu_2*i*PrMgLi (0.35)	Toluene	−10°C, 2.5 h	53
10	Bu_2*i*PrMgLi (0.35)	THF	−10°C, 2.5 h	61

of Bu_3MgLi (699 and 733 cm^{-1}) were observed, at higher temperatures (between −40 and −10°C). As observed by Iida and Mase through ^1H and ^{13}C NMR,[13m] the IR experiment showed the existence of a single species, distinctly different from either BuMgCl or BuLi.

The reaction of commercial 3-bromoquinoline (**1**) using Bu_3MgLi (0.35 equiv.) in toluene at −10°C, as described for the bromine–magnesium exchange of 2,6-dibromopyridine,[13m] followed by trapping with benzaldehyde (1 h at −10°C and 18 h at rt) generated, after hydrolysis, the alcohol **2a** in 65% yield. The first step of the reaction was then optimized using other solvents and bases, under different conditions (Scheme 1, Table 1).

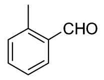
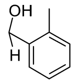
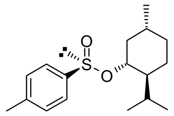
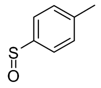
It was noted that the yields largely depend on the amount of base used. Whereas 65% of **2a** was obtained on exposure to 0.35 equiv. of Bu_3MgLi, very poor yields were observed using 0.66 and 1.0 equiv. In the latter cases, quinolines butylated at C2 and C4 were formed, due to nucleophilic addition reactions of residual butylmagnesium species to the ring (entries 1–3). Obviously, accurate charges of BuMgCl and BuLi are necessary to obtain reliable yields. The exchange reaction is still feasible at rt or at reflux instead of −10°C, however greater amounts of butylated quinolines are obtained (entries 4–5). Performing the reaction in other environments showed polar solvents such as THF, methyl *tert*-butyl ether (MTBE), and diethyl ether can be used; THF being the most efficient (entries 6–8). The attempted use of Bu_2*i*PrMgLi[16] gave greater amounts of alkylated side products (entries 9–10).

The reaction proceeded well when 0.35 equiv. of Bu_3MgLi was used, with all three alkyl groups in the base participate in the magnesium–bromine exchange. As the species formed is rather stable in toluene, even at reflux (entry 5), a complex **1a** (assumed to be lithium tri(3-quinolinyl)magnesiate) rather than a mixture of bis(3-quinolinyl)magnesium and 3-quinolinyllithium was postulated. This was supported by IR spectroscopic experiments. Indeed, when Bu_3MgLi was treated with 3-bromoquinoline (**1**) at −10°C, the disappearance of the base (699 and 733 cm^{-1}) was associated with the appearance of the complex **1a** (1270 and 1336 cm^{-1}),[17] which was next consumed by benzaldehyde (Fig. 1), while 3-quinolinyllithium[18] (1065 and 1254 cm^{-1}), 3-quinolinylmagnesium bromide[19] (1262 cm^{-1}) and



Scheme 2.

Table 2. Quenching of **1a**

Entry	Electrophile	E	Product	Yield (%)[a]
1	PhCHO	CH(OH) Ph	**2a**	89, 65[b]
2			**2b**	44
3	DMF	CHO	**2c**	75[b]
4	CO_2	CO_2H	**2d**	46
5	I_2	I	**2e**	81, 76[b]
6	PhSSPh	SPh	**2f**	44[b]
7			**2g**	55[b]

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[a] Isolated yields based on **1**.
[b] Using toluene instead of THF.

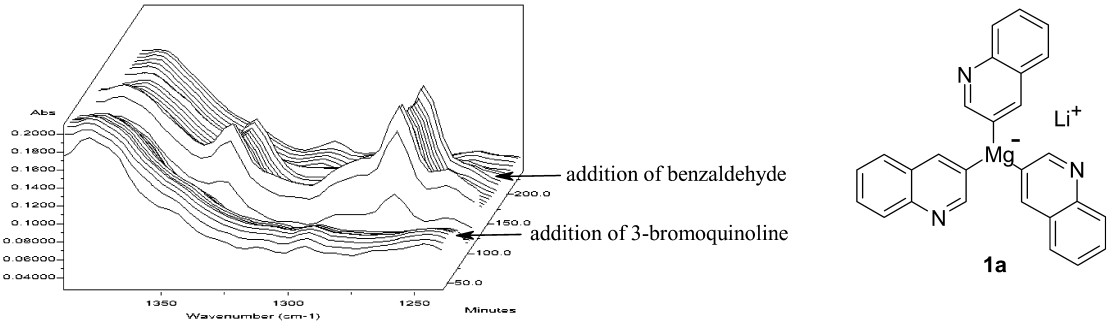
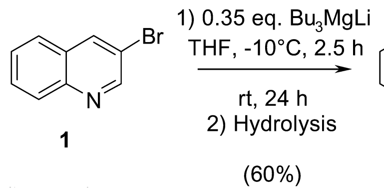


Figure 1. Three-dimensional infrared profile for the formation and consumption of **1a**.



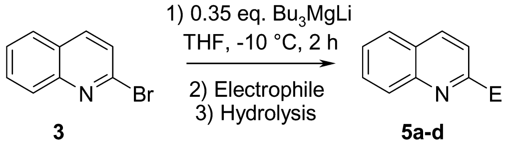
Scheme 3.

bis(3-quinolinyl)magnesium[20] (1073 cm^{-1}) show different absorbances.

The procedure being optimized, a series of electrophiles was used to quench the compound **1a**. Benzaldehydes, dimethylformamide, carbon dioxide, iodine, diphenyl disulfide and menthyl 4-toluenesulfinate afforded the alcohols **2a–b**, the aldehyde **2c**, the carboxylic acid **2d**, the iodide **2e**, the sulfide **2f** and the sulfoxide **2g**, respectively (Scheme 2, Table 2).

Since the reaction with benzaldehyde (entry 1) proceeds well, a steric hindrance effect could explain the lower yield obtained with 2-tolualdehyde (entry 2). Enolizable carbonyl compounds such as acetaldehyde, acetone and 3-pentanone did not furnish the corresponding alcohols (only quinoline was isolated). The reaction with ketones such as benzophenone failed too; quinoline and benzhydrol were isolated, probably through a reduction in the presence of **1a**. Dimethylformamide (entry 3) readily reacts, as observed by Iida and Mase in the pyridine series.[13m] The yield obtained for the amino acid **2d** (entry 4) largely depends on the isolation process. Iodine (entry 5), diphenyl disulfide (entry 6) and menthyl 4-toluenesulfinate (entry 7) could also be used. Of particular importance to rationalize the variable results, the reaction conducted in THF without electrophile (except bromobutane generated in the exchange step) gave 3-butylquinoline (**2h**) in 60% yield (Scheme 3).

The bromine–magnesium exchange reaction was then carried out on 2- and 4-bromoquinolines (**3–4**)[21] using THF as a solvent, under the same conditions. The reaction of 2-bromoquinoline (**3**) and subsequent quenching of the intermediate **3a** with benzaldehyde (entry 1), 3-pentanone (entry 2), iodine (entry 3) and diphenyl disulfide (entry 4) provided the alcohols **5a–b**, the iodide **5c** and the sulfide **5d**, respectively, in low to medium yields (Scheme 4, Table 3).



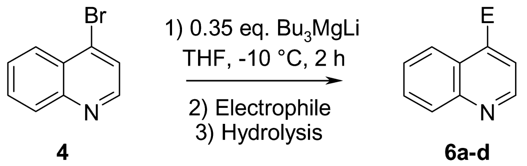
Scheme 4.

Table 3. Quenching of **3a**

Entry	Electrophile	E	Product	Yield (%)[a]
1	PhCHO	CH(OH)Ph	**5a**	39, 18[b]
2	EtCOEt	$C(OH)Et_2$	**5b**	33
3	I_2	I	**5c**	49
4	PhSSPh	SPh	**5d**	15

[a] Isolated yields based on **3**.

[b] Using toluene instead of THF.



Scheme 5.

Table 4. Quenching of **4a**

Entry	Electrophile	E	Product	Yield (%)[a]
1	PhCHO	CH(OH)Ph	**6a**	28
2	CO_2	CO_2H	**6b**	39
3	I_2	I	**6c**	57
4	PhSSPh	SPh	**6d**	47

[a] Isolated yields based on **4**.

The bromine–magnesium exchange step being slower,[22] more side products are formed through addition reactions of unreacted butylmagnesium species to the quinoline ring.[23] Interestingly, the enolizable 3-pentanone (entry 2) gave the expected alcohol, albeit in a low yield of 33%, while hexanal and benzophenone failed.

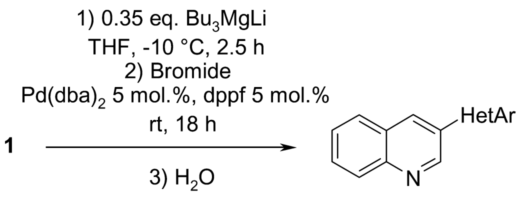
The behaviour of 4-bromoquinoline (**4**) is similar, as exemplified by trapping **4a** with electrophiles to produce the expected alcohol **6a**, the carboxylic acid **6b**, the iodide **6c** and the sulfide **6d** in moderate yields (Scheme 5, Table 4).

Thus, the lithium tri(quinolinyl)magnesates **1a**, **3a** and **4a**, derived from 2-, 3- and 4-bromoquinolines (**1**, **3** and **4**), were prepared and intercepted with various electrophiles.

It was then interesting to study whether an access to arylquinolines via these species was possible. To this end, the intermediates **1a**, **3a** and **4a** were each subjected to transition metal-catalyzed couplings with heteroaromatic halides. A survey of the literature revealed that lithium arylzincates have been involved in palladium catalyzed couplings with aryl iodides in modest yields.[7] Conversely, to our knowledge, studies concerning the use of lithium arylmagnesates have not been reported. The reactions of arylmagnesium halides with aryl chlorides, bromides or iodides are possible at rt under palladium catalysis.[24] Nickel, which is harder than palladium, was most often chosen for chlorides[24f,25] and fluorides,[26] which are harder than bromides and iodides. Recently, iron has been found to be efficient for coupling reactions with chlorides.[27]

Indeed, the coupling experiments conducted under nickel catalysis between **1a**, prepared in THF, and heteroaromatic bromides were unsuccessful. On the other hand, the reactions could be achieved when 5 mol% of bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were used,[24e–g,28] and the 3-arylquinolines **7a–k** were obtained (Scheme 6, Table 5).

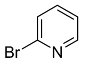
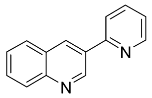
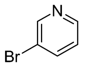
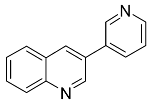
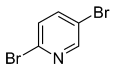
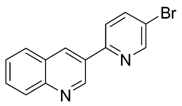
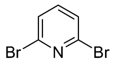
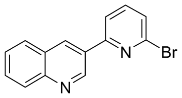
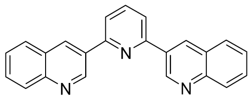
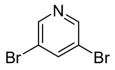
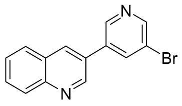
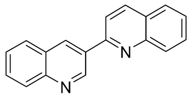
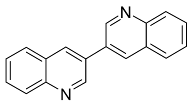
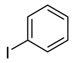
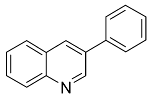
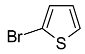
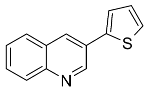
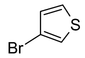
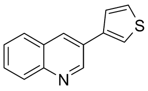
As the step to provide **1a** proceeds in 85–90% yield, the low to modest yields observed are mainly due to the coupling



7a-k

Scheme 6.

Table 5. Coupling of **1a** with bromides

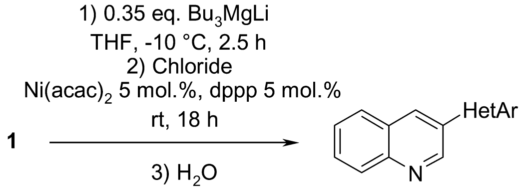
Entry	Bromide	Product	Yield (%)[a]
1		**7a**: 	56, 39,[b] 25[c]
2		**7b**: 	35
3		**7c**: 	53
4		**7d**: 	29, 10[d]
		7e: 	22, 37[d]
5		**7f**: 	12
6	**3**	**7g**: 	51
7	**1**	**7h**: 	45
8		**7i**: 	29, 16[b]
9		**7j**: 	24
10		**7k**: 	15

[a] Isolated yields based on **1**.
[b] Using PPh_3 10 mol% instead of dppf.
[c] Using $PdCl_2$ instead of $Pd(dba)_2$.
[d] Using 0.5 equiv. of 2,6-dibromopyridine.

step. It can be mentioned, as pointed out by Kumada,[28a] that dppf is a more convenient ligand than PPh_3 (entries 1, 8); dba was also found to play an important role (entry 1).[28b] More importantly, the reactivity of the halide involved is crucial since the formation of 3-butylquinoline (**2h**) competes with the cross-coupling reaction.[29] The best results were observed with π-deficient substrates such as bromopyridines and bromoquinolines, for which the oxidative addition step is easier (entries 1–7). The position of the bromine atom on the ring too has a pronounced effect on the yields, the results being better for 2-bromo substrates, as noted by Pridgen for Kharasch cross-couplings in the pyridine series.[30] Consequently, the reaction with 2,5-dibromopyridine is 100% regioselective at C2 (entry 3). With symmetrical dibromopyridines, a single coupling was observed for 3,5-dibromopyridine (entry 5), whereas the mono- and bis-coupled products were obtained for the more reactive 2,6-dibromopyridine (entry 4). Lower yields were obtained with less activated substrates of the benzene (entry 8) and the thiophene (entries 9, 10) series.

The reactions with aryl chlorides were then investigated. Since our first experiments with iron-catalyzed cross-couplings did not appear promising (only homocoupling was observed under the conditions described by Fürstner[27b]), we turned our attention to nickel catalysis. The tandem bis(acetylacetonate)nickel(II) ($Ni(acac)_2$)–1,3-bis(diphenylphosphino)propane (dppp) allowed the 3-arylquinolines **7a**,**b**,**g**,**l**,**m** to be synthesized (Scheme 7, Table 6).

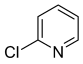
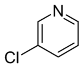
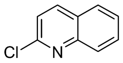
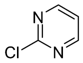
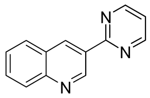
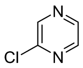
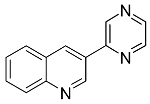
One complication being that the lithium tri(quinolinyl)-magnesate **1a** reacts with bromobutane, the results reflect the lower reactivity of chlorides, when compared to bromides. The use of nickel in the presence of dppp



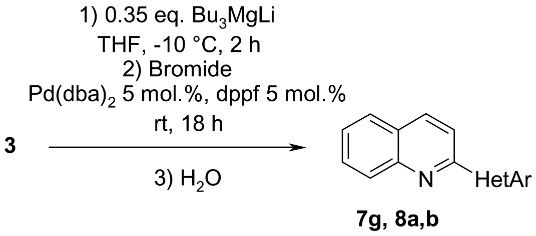
7a,b,g,l,m

Scheme 7.

Table 6. Coupling of **1a** with chlorides

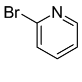
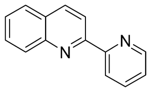
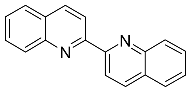
Entry	Chloride	Product	Yield (%)[a]
1		**7a**	18, 21,[b] 0[c]
2		**7b**	8
3		**7g**	0
4		**7l**: 	32
5		**7m**: 	24

[a] Isolated yields based on **1**.
[b] After reflux for 3 h.
[c] Using 1,2-bis(diphenylphosphino)ethane or dpdf instead of dppp.

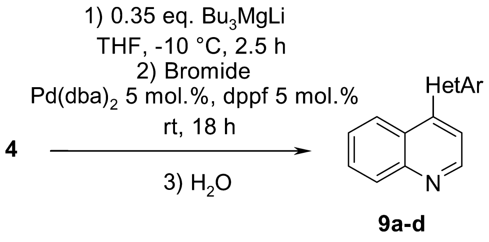


Scheme 8.

Table 7. Coupling of **3a** with bromides

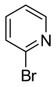
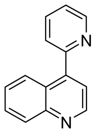
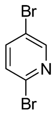
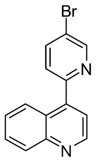
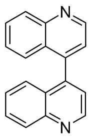
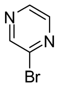
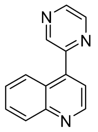
Entry	Bromide	Product	Yield (%)[a]
1		**8a**: 	28
2	**3**	**8b**: 	27
3	**1**	**7g**	11, 13[b]

[a] Isolated yields based on **3**.
[b] After reflux for 5 h.



Scheme 9.

Table 8. Coupling of **4a** with bromides

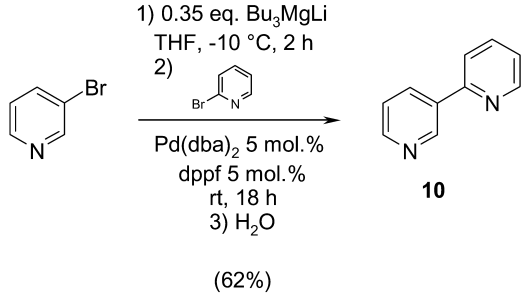
Entry	Bromide	Product	Yield (%)[a]
1		**9a**: 	43
2		**9b**: 	48
3	**4**	**9c**: 	<5
4		**9d**: 	23

[a] Isolated yields based on **4**.

(found to be the best ligand, as observed for the Karasch cross-couplings)[2b,24c,e–g,25,28a,30,31] could help to favour the insertion step, but the yields of the whole process remain modest. The importance of the substrate used (better yields with diazines (entries 4, 5) than azines (entries 1–3)) and the position of the chlorine atom on the ring (entries 1, 2) was clearly evidenced.

To evaluate the scope of this reaction, it was applied to the lithium tri(quinolinyl)magnesates **3a** (Scheme 8, Table 7) and **4a** (Scheme 9, Table 8).

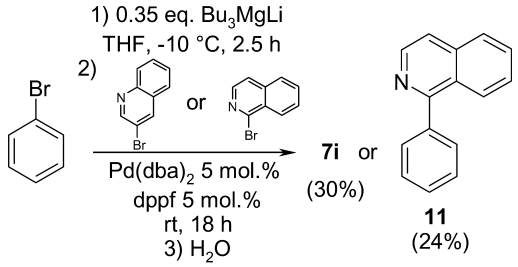
Lower yields were observed for the syntheses of **7g**, **8a**,**b** and **9a–d**, mainly due to the preparation step of the intermediates **3a** and **4a**. A steric hindrance effect can be put forward in some cases (e.g. Table 8, entry 3), as already evoked in Kharasch cross-couplings.[30]



Scheme 10.

The reaction was performed in the pyridine and benzene series under the same conditions. Starting from 3-bromopyridine, 'one pot' bromine–magnesium exchange, followed by coupling of the lithium tri(pyridinyl)magnesate generated with 2-bromopyridine, afforded the bipyridine **10** in a yield comparable to those obtained for the Kharasch cross-couplings of 3-pyridinylmagnesium chlorides[24f] (Scheme 10).

The procedure was similarly effected starting from bromobenzene, to afford the phenyl azines **7i** and **11**, albeit in a poor yield due to the conditions used for the preparation of the lithium magnesate[32] (Scheme 11).



Scheme 11.

3. Conclusion

We have demonstrated that a magnesium ate complex, Bu_3MgLi, induces the bromine–magnesium exchange of 2-, 3- and 4-bromoquinolines, giving the corresponding lithium tri(quinolinyl)magnesates. These were either intercepted with various electrophiles or involved in metal-catalyzed coupling reactions with aromatic halides in a one pot procedure. Though the yields are not high, this method is interesting since it avoids a preliminary synthesis of the 'organometallic' substrate, usually at low temperatures via its corresponding lithio compound. Another advantage of this methodology is the relative stabilities of these organometallic species: the bromine–lithium exchange[5] has to be performed at low temperatures to prevent side reactions whereas the bromine–magnesium exchange proceeds at −10°C. The yields obtained are often analogous to those observed during bromine–lithium exchange reactions[5] or cross-couplings through quinolinylboranes.[33]

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Bruker AM 300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). Mass spectra were recorded with a Jeol JMS-AX500 spectrometer, and the molecular peak is given. IR spectra were taken on a Perkin–Elmer FT IR 205 spectrometer, and main IR absorptions are given in cm^{-1}. Elemental analyses were performed on a Carlo Erba 1106 apparatus.

Starting materials. THF was distilled from benzophenone/Na. Toluene was dried over P_2O_5. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[34] Reactions were carried out under dry N_2. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. BuMgCl (2.0 M) in Et_2O and BuLi (1.6 M) in hexane were purchased from Aldrich. 2- and 4-Bromoquinolines (**3**, **4**) were prepared from 2- and 4-hydroxyquinolines, respectively.[21] 1-Bromoisoquinoline was prepared from isoquinoline *N*-oxide.[35] 3-Bromoquinoline (**1**), $Pd(dba)_2$ and $Ni(acac)_2$ were supplied by Acros, dppf by Avocado and dppp by Lancaster. $Pd(PPh_3)_4$[36] was prepared according to described procedures. Petrol refers to petroleum ether (bp 40–60°C).

Unless otherwise noted, the reaction mixture was diluted with AcOEt (50 mL) after the reaction. The organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and the crude compound was chromatographed on a silica gel column (eluent is given in the product description).

4.2. General procedure 1: 3-substituted quinolines 2a–g by bromine–magnesium exchange of 1 and subsequent trapping with electrophiles

To the solvent (2 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, a solution of 3-bromoquinoline (**1**, 0.23 mL, 1.7 mmol) in the solvent (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2.5 h. The electrophile (1.7 mmol) was then added at −10°C; the mixture was stirred at this temperature for 1 h and at rt for 18 h before addition of water (0.5 mL).

4.2.1. α-Phenyl-3-quinolinemethanol (2a). The general procedure 1, using PhCHO (0.17 mL), gave 89% (solvent: THF) of **2a** (eluent: CH_2Cl_2/AcOEt 90:10): mp 138–140°C (lit.[5d] 136–138°C); the IR and NMR data are in accordance with those of the literature.[5d]

4.2.2. α-(2-Methylphenyl)-3-quinolinemethanol (2b). The general procedure 1, using 2-methylbenzaldehyde (0.20 g), gave 44% (solvent: THF) of **2b** (eluent: CH_2Cl_2/AcOEt 90:10): mp 134°C; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H, Me), 4.20 (s, 1H, OH), 6.05 (s, 1H, CH(OH)), 7.03 (m, 1H, $H_{5'}$), 7.12 (m, 2H, $H_{3',4'}$), 7.38 (m, 1H, $H_{6'}$), 7.43 (m, 1H, H_6), 7.55 (m, 1H, H_7), 7.62 (d, 1H, J=8.3 Hz, H_5), 7.92 (d, 1H, J=8.3 Hz, H_8), 7.95 (d, 1H, J=1.9 Hz, H_4), 8.57 (d, 1H, J=1.9 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 19.8 (Me), 71.5

(CH(OH)), 126.8 (C_3), 127.1 ($C_{6'}$), 127.2 (C_6), 128.1 ($C_{4'}$), 128.3 (C_5), 129.1 (C_b), 129.9 (C_7), 130.0 (C_8), 131.1 (C_4), 134.1 ($C_{5'}$), 135.8 ($C_{3'}$), 136.5 ($C_{1'}$), 141.1 ($C_{2'}$), 147.4 (C_a), 150.7 (C_2); IR (KBr) ν 3147, 2832, 1457, 1331, 1231, 819, 699 cm^{-1}. Anal. calcd for $C_{17}H_{15}NO$ (249.32): C, 81.90; H, 6.06; N, 5.62. Found: C, 81.63; H, 6.04; N, 5.43%.

4.2.3. 3-Quinolinecarboxaldehyde (2c). The general procedure 1, using DMF (0.13 mL), gave 75% (solvent: toluene) of **2c** (eluent: CH_2Cl_2/AcOEt 90:10). The physical and spectral data are analogous to those obtained for a commercial sample (Aldrich).

4.2.4. 3-Quinolinecarboxylic acid (2d). The general procedure 1, using an excess of freshly crushed dry ice (in this case, the aqueous phase obtained after evaporation of the residue to dryness and addition of water (3 mL) was washed with CH_2Cl_2 (10 mL) and acidified to pH 1 using a 5% aqueous solution of hydrochloric acid; **2d** was then recovered after filtration and drying under vacuum), gave 46% (solvent: THF) of **2d**. The physical and spectral data are analogous to those obtained for a commercial sample (Aldrich).

4.2.5. 3-Iodoquinoline (2e).[37] The general procedure 1, using a solution of I_2 (0.43 g) in THF (3 mL) (in this case, the reaction mixture was treated with 0.3 g of $Na_2S_2O_3$), gave 81% (solvent: THF) of **2e** (eluent: petrol/AcOEt 90:10): mp 48°C; ^1H NMR ($CDCl_3$) δ 7.7 (m, 3H, $H_{5,6,7}$), 7.98 (d, 1H, J=7.5 Hz, H_8), 8.46 (d, 1H, J=1.9 Hz, H_4), 8.96 (d, 1H, J=1.9 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 90.2 (C_3), 127.2 (C_6), 130.2 (C_5), 130.4 (C_8), 137.6 (C_b), 144.1 (C_7), 146.7 (C_4), 151.8 (C_a), 156.0 (C_2); IR (KBr) ν 1573, 1489, 1348, 1312, 1122, 1071, 937, 885, 778, 745 cm^{-1}. Anal. calcd for C_9H_6IN (255.06): C, 42.38; H, 2.37; N, 5.49. Found: C, 42.61; H, 2.37; N, 5.61%.

4.2.6. 3-(Phenylthio)quinoline (2f). The general procedure 1, using a solution of PhSSPh (0.37 g) in toluene (3 mL), gave 44% (solvent: toluene) of **2f** (eluent: petrol/AcOEt 90:10): mp 88°C (lit.[38] 79–80°C); the ^1H NMR data are in accordance with those of the literature;[38] ^{13}C NMR ($CDCl_3$) δ 127.6 ($C_{2',6'}$), 127.7 (C_3), 128.1 (C_6), 128.1 ($C_{3',5'}$), 128.6 ($C_{1'}$), 129.9 ($C_{4'}$), 130.0 (C_5), 130.4 (C_b), 131.7 (C_7), 134.7 (C_8), 137.5 (C_4), 147.0 (C_a), 152.6 (C_2); IR (KBr) ν 3055, 2926, 1577, 1475, 1073, 910, 785, 743, 689 cm^{-1}. Anal. calcd for $C_{15}H_{11}NS$ (237.33): C, 75.92; H, 4.67; N, 5.90; S, 13.51. Found: C, 75.94; H, 4.84; N, 5.96; S, 13.38%.

4.2.7. 3-((4-Methylphenyl)sulfinyl)quinoline (2g). The general procedure 1, using (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-4-toluenesulfinate (0.50 g), gave 55% (solvent: toluene) of **2g** (eluent: CH_2Cl_2/Et_2O 90:10): mp 126°C; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H, Me), 7.21 (m, 2H, Ph), 7.55 (m, 3H, H_6 and Ph), 7.8 (m, 2H, $H_{5,7}$), 8.05 (d, 1H, J=8.7 Hz, H_8), 8.53 (d, 1H, J=2.2 Hz, H_4), 8.76 (d, 1H, J=2.2 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 21.8 (Me), 125.6 ($C_{2',6'}$), 127.7 (C_3), 128.3 (C_b), 128.8 (C_6), 129.9 ($C_{3',5'}$), 130.7 (C_5), 131.7 (C_7), 133.2 (C_4), 139.5 (C_8), 141.7 (C_a), 142.9 ($C_{1'}$), 146.2 (C_2), 149.1 ($C_{4'}$); IR (KBr) ν 2919, 1493, 1358, 1086, 1045, 1015, 956, 808, 752, 631 cm^{-1}. Anal. calcd for $C_{16}H_{13}NOS$ (267.35): C, 71.88; H, 4.90; N, 5.24; S, 11.99. Found: C, 71.89; H, 4.93; N, 5.24; S, 11.72%.

4.3. General procedure 2: 2-substituted quinolines 5a–d by bromine–magnesium exchange of 3 and subsequent trapping with electrophiles

To THF (2 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, a solution of 2-bromoquinoline (**3**, 0.35 g, 1.7 mmol) in THF (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2 h. The electrophile (1.7 mmol) was then added at −10°C; the mixture was stirred at this temperature for 1 h and at rt for 18 h before addition of water (0.5 mL).

4.3.1. α-Phenyl-2-quinolinemethanol (5a). The general procedure 2, using PhCHO (0.17 mL), gave 39% of **5a** (eluent: CH_2Cl_2/AcOEt 90:10): mp 96°C; the ^1H NMR data are in accordance with those of the literature;[6] ^{13}C NMR ($CDCl_3$) δ 75.6 (CH(OH)), 119.7 (C_3), 127.8 (C_8), 127.9 (C_b), 128.0 ($C_{3',5'}$), 128.4 (C_5), 129.0 ($C_{2',6'}$), 129.2 (C_6), 129.7 (C_7), 130.2 ($C_{4'}$), 137.4 (C_4), 141.4 ($C_{1'}$), 146.4 (C_a), 160.9 (C_2); IR (KBr) ν 3053, 1664, 1599, 1445, 1318, 1293, 1168, 967, 784, 754, 690, 621 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO$ (235.29): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.46; H, 5.43; N, 5.67%.

4.3.2. α,α-Diethyl-2-quinolinemethanol (5b). The general procedure 2, using an excess of EtCOEt (2 mL), gave 33% of **5b** (eluent: CH_2Cl_2/AcOEt 90:10); the physical and spectral data are in accordance with those of the literature.[39] Anal. calcd for $C_{14}H_{17}NO$ (215.30): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.34; H, 7.81; N, 6.67%.

4.3.3. 2-Iodoquinoline (5c).[40] The general procedure 2, using a solution of I_2 (0.43 g) in THF (3 mL) (in this case, the reaction mixture was treated with 0.3 g of $Na_2S_2O_3$), gave 49% of **5c** (eluent: CH_2Cl_2/AcOEt 90:10): mp 52–53°C; ^1H NMR ($CDCl_3$) δ 7.45 (m, 1H, H_6), 7.6 (m, 4H, $H_{3,4,5,7}$), 7.95 (d, 1H, J=8.7 Hz, H_8); ^{13}C NMR ($CDCl_3$) δ 119.4 (C_2), 127.5 (C_b), 128.2 (C_6), 129.2 (C_5), 130.3 (C_8), 130.6 (C_3), 132.3 (C_7), 137.4 (C_4), 149.9 (C_a); IR (KBr) ν 1579, 1495, 1347, 1343, 1116, 1049, 937 cm^{-1}. Anal. calcd for C_9H_6IN (255.06): C, 42.38; H, 2.37; N, 5.49. Found: C, 42.46; H, 2.64; N, 5.64%.

4.3.4. 2-(Phenylthio)quinoline (5d). The general procedure 2, using a solution of PhSSPh (0.37 g) in THF (3 mL), gave 15% of **5d** (eluent: CH_2Cl_2/AcOEt 90:10). The physical and spectral data are analogous to those obtained for a commercial sample (Acros).

4.4. General procedure 3: 4-substituted quinolines 6a–d by bromine–magnesium exchange of 4 and subsequent trapping with electrophiles

To THF (2 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, a solution of 4-bromoquinoline (**4**, 0.35 g, 1.7 mmol) in THF (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2.5 h. The electrophile (1.7 mmol) was then added at −10°C; the mixture was stirred at this temperature for 1 h and at rt for 18 h before addition of water (0.5 mL).

4.4.1. α-Phenyl-4-quinolinemethanol (6a).[41] The general procedure 3, using PhCHO (0.17 mL), gave 28% of **6a**

(eluent: CH_2Cl_2/AcOEt 90:10): mp 118°C; ^1H NMR ($CDCl_3$) δ 3.50 (s, 1H, OH), 6.42 (s, 1H, CH(OH)), 7.18 (d, 1H, J=4.5 Hz, H_3), 7.3 (m, 5H, $H_{2',3',4',5',6'}$), 7.55 (m, 1H, H_6), 7.60 (d, 1H, J=7.5 Hz, H_5), 7.83 (m, 1H, H_7), 7.99 (d, 1H, J=8.7 Hz, H_8), 8.73 (d, 1H, J=4.5 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 73.0 (CH(OH)), 118.9 (C_3), 124.2 (C_5), 126.1 (C_b), 126.3 (C_7), 126.7 (C_6), 126.9 (C_8), 127.7 ($C_{2',6'}$), 129.2 ($C_{3',5'}$), 129.5 ($C_{1'}$), 130.3 ($C_{4'}$), 142.5 (C_a), 149.1 (C_4), 150.5 (C_2); IR (KBr) ν 3058, 2817, 1437, 1325, 1198, 787 cm^{-1}. Anal. calcd for $C_{16}H_{13}NO$ (235.29): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.39; H, 5.46; N, 5.79%.

4.4.2. 4-Quinolinecarboxylic acid (6b). The general procedure 3, using an excess of freshly crushed dry ice (in this case, the aqueous phase obtained after evaporation of the residue to dryness and addition of water (3 mL) was washed with CH_2Cl_2 (10 mL) and acidified to pH 1 using a 5% aqueous solution of hydrochloric acid; **6b** was then recovered after filtration and drying under vacuum), gave 39% of **6b**. The physical and spectral data are analogous to those obtained for a commercial sample (Aldrich).

4.4.3. 4-Iodoquinoline (6c).[42] The general procedure 3, using a solution of I_2 (0.43 g) in THF (3 mL) (in this case, the reaction mixture was treated with 0.3 g of $Na_2S_2O_3$), gave 57% of **6c** (eluent: CH_2Cl_2/AcOEt 90:10): mp 90°C; ^1H NMR ($CDCl_3$) δ 7.48 (m, 1H, H_6), 7.61 (m, 1H, H_7), 7.84 (d, 1H, J=4.3 Hz, H_3), 7.88 (d, 1H, J=8.3 Hz, H_8), 7.92 (d, 1H, J=7.1 Hz, H_5), 8.32 (d, 1H, J=4.3 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 112.4 (C_3), 127.1 (C_b), 128.5 (C_5), 130.5 (C_6), 130.7 (C_8), 132.1 (C_7), 132.9 (C_4), 148.5 (C_a), 150.1 (C_2); IR (KBr) ν 3398, 3066, 1627, 1575, 1568, 1413, 1197, 1056, 965, 837, 663 cm^{-1}. Anal. calcd for C_9H_6IN (255.06): C, 42.38; H, 2.37; N, 5.49. Found: C, 42.34; H, 2.34; N, 5.18%.

4.4.4. 4-(Phenylthio)quinoline (6d). The general procedure 3, using a solution of PhSSPh (0.37 g) in THF (3 mL), gave 47% of **6d** (eluent: CH_2Cl_2/AcOEt 90:10); the physical and spectral data are in accordance with those of the literature;[43] IR (KBr) ν 3048, 2933, 1537, 1466, 1071, 832, 689 cm^{-1}.

4.5. General procedure 4: 3-substituted quinolines 7a–k by bromine–magnesium exchange of 1 and subsequent cross-coupling with bromides and iodides

To THF (4 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, 3-bromoquinoline (**1**, 0.23 mL, 1.7 mmol) in THF (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2 h. A solution of the halide (1.7 mmol) in THF (3 mL), $Pd(dba)_2$ (48 mg, 83 μmol) and dppf (47 mg, 83 μmol) were successively added at −10°C; the mixture was stirred for 1 h at this temperature and for 18 h at rt before addition of an aqueous saturated NH_4Cl solution (0.5 mL).

4.5.1. 3-(2-Pyridinyl)quinoline (7a). The general procedure 4, using 2-bromopyridine (0.16 mL), gave 57% of **7a** (eluent: CH_2Cl_2/Et_2O 80:20): mp 100°C (lit.[33a] 99–100°C); the ^1H NMR data are in accordance with those of the literature;[33a] ^{13}C NMR ($CDCl_3$) δ 121.1 ($C_{3'}$), 123.2 ($C_{5'}$), 127.4 (C_6), 128.2 (C_5), 128.9 (C_b), 129.6 (C_7), 130.3 (C_8), 132.2 (C_3), 134.2 (C_4), 137.4 ($C_{4'}$), 148.5 (C_a), 149.6 ($C_{6'}$), 150.5 (C_2), 155.1 ($C_{2'}$); IR (KBr) ν 3040, 1591, 1567, 1495, 1407, 1344, 1303, 1095, 992, 959, 927, 710, 738, 619 cm^{-1}. Anal. calcd for $C_{14}H_{10}N_2$ (206.25): C, 81.53; H, 4.89; N, 13.58. Found: C, 81.28; H, 4.71; N, 13.53%.

4.5.2. 3-(3-Pyridinyl)quinoline (7b). The general procedure 4, using 3-bromopyridine (0.16 mL), gave 35% of **7b** (eluent: CH_2Cl_2/Et_2O 80:20): mp 127°C (lit.[33a] 128–129°C); the ^1H NMR data are in accordance with those of the literature;[33a] ^{13}C NMR ($CDCl_3$) δ 124.3 (C_6), 127.7 (C_3), 127.8 ($C_{5'}$), 128.0 (C_b), 128.1 (C_7), 128.2 ($C_{3'}$), 128.5 (C_8), 129.6 (C_4), 129.7 (C_5), 130.4 (C_a), 134.1 ($C_{4'}$), 135.1 (C_2), 148.8 ($C_{6'}$), 149.6 ($C_{2'}$); IR (KBr) ν 3041, 2924, 2853, 1567, 1495, 1338, 1186, 1022, 952, 815, 758, 700 cm^{-1}.

4.5.3. 3-(5-Bromo-2-pyridinyl)quinoline (7c). The general procedure 4, using 2,5-dibromopyridine (0.40 g), gave 53% of **7c** (eluent: CH_2Cl_2/Et_2O 80:20): mp 150°C; ^1H NMR ($CDCl_3$) δ 7.46 (m, 1H, H_6), 7.75 (m, 2H, $H_{5,7}$), 7.79 (m, 2H, $H_{8,4'}$), 8.03 (d, 1H, J=8.3 Hz, $H_{3'}$), 8.58 (d, 1H, J=2.2 Hz, H_4), 8.68 (d, 1H, J=3.2 Hz, $H_{6'}$), 9.34 (d, 1H, J=2.2 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 120.5 ($C_{5'}$), 122.1 ($C_{3'}$), 126.9 (C_6), 127.6 (C_5), 128.2 (C_b), 129.6 (C_7), 129.8 (C_8), 131.0 (C_3), 134.1 (C_4), 139.9 ($C_{4'}$), 148.6 (C_a), 150.8 ($C_{2'}$), 151.5 ($C_{6'}$), 153.5 (C_2); IR (KBr) ν 3053, 1573, 1494, 1355, 1122, 1092, 1005, 844, 789, 760, 621 cm^{-1}. Anal. calcd for $C_{14}H_9BrN_2$ (285.15): C, 58.97; H, 3.18; N, 9.82. Found: C, 58.83; H, 3.16; N, 9.54%.

4.5.4. 3-(6-Bromo-2-pyridinyl)quinoline (7d) and 2,6-bis-(3-quinolinyl)pyridine (7e). The general procedure 4, using 2,6-dibromopyridine (0.40 g), gave 29% of **7d** (eluent: CH_2Cl_2/Et_2O 80:20): mp 177°C; ^1H NMR ($CDCl_3$) δ 7.43 (d, 1H, J=7.9 Hz, $H_{5'}$), 7.52 (m, 1H, H_4), 7.65 (m, 2H, $H_{6,7}$), 7.79 (d, 1H, J=7.5 Hz, $H_{3'}$), 7.87 (d, 1H, J=7.7 Hz, H_5), 8.08 (d, 1H, J=8.0 Hz, H_8), 8.74 (d, 1H, J=1.7 Hz, H_4), 9.40 (d, 1H, J=1.7 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 119.7 ($C_{3'}$), 127.6 (C_6), 127.6 (C_5), 128.1 ($C_{5'}$), 129.1 (C_b), 129.7 (C_7), 130.8 (C_8), 134.8 (C_4), 130.5 (C_3), 139.7 ($C_{4'}$), 143.1 ($C_{6'}$), 148.0 (C_a), 149.1 (C_2), 156.3 (C'_2); IR (KBr) ν 3061, 579, 1439, 1123, 984, 797, 729 cm^{-1}. Anal. calcd for $C_{14}H_9BrN_2$ (285.15): C, 58.97; H, 3.18; N, 9.82. Found: C, 58.87; H, 3.26; N, 9.53%, and 22% of **7e** (eluent: CH_2Cl_2/Et_2O 50:50): mp 220°C; ^1H NMR ($CDCl_3$) δ 7.55 (m, 2H, $H_{6'}$), 7.72 (m, 2H, $H_{7'}$), 7.90 (m, 5H, $H_{3,4,5,5'}$), 8.12 (d, 2H, J=8.3 Hz, $H_{8'}$), 8.86 (d, 2H, J=2.1 Hz, $H_{4'}$), 9.66 (d, 2H, J=2.1 Hz, $H_{2'}$); ^{13}C NMR ($CDCl_3$) δ 120.3 ($C_{3,5}$), 127.5 ($2C_{6'}$), 127.8 ($2C_{5'}$), 128.9 ($2C_{b'}$), 129.3 ($2C_{7'}$), 129.7 ($2C_{8'}$), 130.5 ($2C_{3'}$), 134.4 ($2C_{4'}$), 138.6 (C_4), 148.7 ($2C_{a'}$), 149.8 ($2C_{2'}$), 155.3 ($C_{2,6}$); IR (KBr) ν 3050, 2923, 1586, 1334, 949, 812 cm^{-1}. Anal. calcd for $C_{23}H_{15}N_3$ (333.40): C, 80.86; H, 4.54; N, 11.60. Found: C, 80.58; H, 4.83; N, 11.32%.

4.5.5. 3-(5-Bromo-3-pyridinyl)quinoline (7f). The general procedure 4, using 3,5-dibromopyridine (0.40 g), gave 12% of **7f** (eluent: CH_2Cl_2/Et_2O 80:20): mp 163°C; ^1H NMR ($CDCl_3$) δ 7.58 (t, 1H, J=8.3 Hz, H_6), 7.74 (m, 1H, H_7), 7.85 (d, 1H, J=8.3 Hz, H_5), 8.10 (m, 2H, $H_{8,6'}$), 8.27 (t, 1H, J=1.9 Hz, $H_{4'}$), 8.68 (d, 1H, J=2.4 Hz, H_4), 8.82 (d, 1H, J=1.9 Hz, $H_{2'}$), 9.06 (d, 1H, J=2.4 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 121.5 ($C_{5'}$), 127.9 (C_6), 128.0 (C_5), 128.5 (C_b), 129.5 (C_8), 129.7 (C_7), 130.7 (C_3), 134.4 (C_4), 135.5 ($C_{3'}$), 137.4 (C$_{6'}$), 146.8 (C$_a$), 148.2 (C$_{2'}$), 149.2 (C$_2$), 150.5 (C$_{4'}$); IR (KBr) ν 3058, 1587, 1493, 1107, 1088, 857, 789, 760 cm^{-1}. Anal. calcd for $C_{14}H_9BrN_2$ (285.15): C, 58.97; H, 3.18; N, 9.82. Found: C, 58.74; H, 3.43; N, 9.74%.

4.5.6. 2,3′-Biquinoline (7g). The general procedure 4, using 2-bromoquinoline (**3**, 0.35 g), gave 51% of **7g** (eluent: CH_2Cl_2/Et_2O 80:20): mp 173°C (lit.[33a] 175–176°C); the ^{1}H NMR data are in accordance with those of the literature;[33a] ^{13}C NMR ($CDCl_3$) δ 119.1 (C$_{3'}$), 127.5 (C$_{b'}$), 128.0 (C$_6$), 128.0 (C$_{6'}$), 129.0 (C$_5$), 129.0 (C$_{5'}$), 129.7 (C$_b$), 130.2 (C$_7$), 130.2 (C$_{7'}$), 130.5 (C$_8$), 130.5 (C$_{8'}$), 130.6 (C$_3$), 137.6 (C$_{4'}$), 137.7 (C$_4$), 147.4 (C$_{a'}$), 148.0 (C$_a$), 150.2 (C$_2$), 154.7 (C$_{2'}$); IR (KBr) ν 3051, 1595, 1506, 1494, 1434, 1406, 1320, 1305, 1289, 1195, 1122, 1045, 1012, 968, 938, 837, 787, 746, 649, 622 cm^{-1}. Anal. calcd for $C_{18}H_{12}N_2$ (256.31): C, 84.35; H, 4.72; N, 10.93. Found: C, 84.11; H, 4.53; N, 10.67%.

4.5.7. 3,3′-Biquinoline (7h). The general procedure 4, using 3-bromoquinoline (**1**, 0.23 mL), gave 45% of **7h** (eluent: CH_2Cl_2/Et_2O 80:20): mp 270°C (lit.[44] 270°C); the ^{1}H NMR data are in accordance with those of the literature;[44] ^{13}C NMR ($CDCl_3$) δ 127.8 (C$_{6,6'}$), 128.3 (C$_{5,5'}$), 128.5 (C$_{b,b'}$), 129.8 (C$_{7,7'}$), 130.4 (C$_{8,8'}$), 131.1 (C$_{3,3'}$), 134.3 (C$_{4,4'}$), 148.0 (C$_{a,a'}$), 149.9 (C$_{2,2'}$); IR (KBr) ν 3042, 2947, 1884, 1573, 1493, 1353, 1320, 1197, 1127, 940, 926, 754, 624 cm^{-1}. Anal. calcd for $C_{18}H_{12}N_2$ (256.31): C, 84.35; H, 4.72; N, 10.93. Found: C, 84.06; H, 4.63; N, 10.82%.

4.5.8. 3-Phenylquinoline (7i). The general procedure 4, using iodobenzene (0.19 mL), gave 29% of **7i** (eluent: CH_2Cl_2/Et_2O 80:20): mp 52°C (lit.[33a] 51–53°C); the NMR data are in accordance with those of the literature;[45] IR (KBr) ν 3058, 1493, 902, 786, 761, 696 cm^{-1}. Anal. calcd for $C_{15}H_{11}N$ (205.26): C, 87.77; H, 5.40; N, 6.82. Found: C, 87.58; H, 5.54; N, 6.69%.

4.5.9. 3-(2-Thienyl)quinoline (7j). The general procedure 4, using 2-bromothiophene (0.14 g), gave 24% of **7j** (eluent: CH_2Cl_2/Et_2O 50:50): mp 66°C; the ^{1}H NMR data are in accordance with those of the literature;[31b] ^{13}C NMR ($CDCl_3$) δ 124.8 (C$_{3'}$), 126.5 (C$_{5'}$), 126.9 (C$_6$), 127.6 (C$_{4'}$), 127.9 (C$_5$), 128.2 (C$_b$), 129.5 (C$_7$), 129.7 (C$_8$), 129.7 (C$_3$), 134.5 (C$_4$), 141.1 (C$_{2'}$), 147.6 (C$_a$), 149.0 (C$_2$); IR (KBr) ν 2930, 2365, 1492, 1430, 1345, 1327, 1280, 1124, 1078, 913, 860, 782, 749, 691 cm^{-1}.

4.5.10. 3-(3-Thienyl)quinoline (7k). The general procedure 4, using 3-bromothiophene (0.14 g), gave 15% of **7k** (eluent: CH_2Cl_2/Et_2O 50:50): mp 86–88°C (lit.[33a] 88–89°C); the ^{1}H NMR data are in accordance with those of the literature;[33a] ^{13}C NMR ($CDCl_3$) δ 122.0 (C$_{2'}$), 126.5 (C$_{4'}$), 126.9 (C$_6$), 127.7 (C$_5$), 128.3 (C$_{5'}$), 128.5 (C$_b$), 129.1 (C$_7$), 129.5 (C$_8$), 129.6 (C$_3$), 134.5 (C$_4$), 139.3 (C$_{3'}$), 147.6 (C$_a$), 149.8 (C$_2$); IR (KBr) ν 3064, 2955, 1667, 1602, 1571, 1494, 1463, 1422, 1378, 1330, 1126, 1087, 1015, 788, 752, 700, 660, 623 cm^{-1}.

4.6. General procedure 5: 3-substituted quinolines 7l–m by bromine–magnesium exchange of 1 and subsequent cross-coupling with chlorides

To THF (4 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, 3-bromoquinoline (**1**, 0.23 mL, 1.7 mmol) in THF (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2 h. A solution of the chloride (1.7 mmol) in THF (3 mL), Ni(acac)$_2$ (21 mg, 83 μmol) and dppp (34 mg, 83 μmol) were successively added at −10°C; the mixture was stirred for 1 h at this temperature and for 18 h at rt before addition of an aqueous saturated NH_4Cl solution (0.5 mL).

4.6.1. 3-(2-Pyrimidinyl)quinoline (7l). The general procedure 5, using 2-chloropyrimidine (0.19 g), gave 32% of **7l** (eluent: CH_2Cl_2/AcOEt 60:40): mp 113°C; ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 1H, H$_{5'}$), 7.50 (m, 1H, H$_7$), 7.69 (m, 1H, H$_6$), 7.88 (d, 1H, J=7.0 Hz, H$_5$), 8.09 (d, 1H, J=8.0 Hz, H$_8$), 8.78 (d, 2H, J=1.5 Hz, H$_{4',6'}$), 9.12 (d, 1H, J=1.0 Hz, H$_4$), 9.85 (d, 1H, J=1.0 Hz, H$_2$); ^{13}C NMR ($CDCl_3$) δ 115.7 (C$_{5'}$), 128.0 (C$_6$), 128.1 (C$_5$), 129.3 (C$_b$), 129.6 (C$_8$), 130.5 (C$_7$), 131.0 (C$_3$), 136.3 (C$_4$), 149.4 (C$_a$), 150.5 (C$_2$), 160.7 (C$_{4',6'}$), 163.4 (C$_{2'}$); IR (KBr) ν 3043, 1560, 1423, 1345, 810, 747 cm^{-1}. Anal. calcd for $C_{13}H_9N_3$ (207.24): C, 75.35; H, 4.38; N, 20.28. Found: C, 75.08; H, 4.26; N, 19.98%.

4.6.2. 3-(2-Pyrazinyl)quinoline (7m). The general procedure 5, using 2-chloropyrazine (0.15 mL), gave 24% of **7m** (eluent: CH_2Cl_2/AcOEt 60:40): mp 146°C; ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 1H, H$_7$), 7.75 (m, 1H, H$_6$), 7.89 (d, 1H, J=8.3 Hz, H$_5$), 8.10 (d, 1H, J=8.0 Hz, H$_8$), 8.55 (d, 1H, J=2.5 Hz, H$_4$), 8.66 (d, 1H, J=1.5 Hz, H$_{6'}$), 8.73 (s, 1H, H$_{3'}$), 9.14 (d, 1H, J=1.5 Hz, H$_{5'}$), 9.51 (d, 1H, J=2.5 Hz, H$_2$); ^{13}C NMR ($CDCl_3$) δ 126.3 (C$_6$), 127.8 (C$_7$), 128.0 (C$_3$), 128.9 (C$_8$), 129.8 (C$_4$), 131.0 (C$_b$), 134.7 (C$_5$), 140.4 (C$_a$), 142.7 (C$_{3'}$), 144.1 (C$_2$), 145.0 (C$_{5'}$), 149.0 (C$_{2'}$), 149.1 (C$_{6'}$); IR (KBr) ν 3038, 2922, 1574, 1495, 1311, 1127, 1071, 1013, 853, 786, 750 cm^{-1}. Anal. calcd for $C_{13}H_9N_3$ (207.24): C, 75.35; H, 4.38; N, 20.28. Found: C, 75.11; H, 4.53; N, 20.02%.

4.7. General procedure 6: 2-substituted quinolines 8a–b by bromine–magnesium exchange of 3 and subsequent cross-coupling with bromides

To THF (4 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, a solution of 2-bromoquinoline (**3**, 0.35 g, 1.7 mmol) in THF (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2 h. A solution of the bromide (1.7 mmol) in THF (3 mL), Pd(dba)$_2$ (48 mg, 83 μmol) and dppf (47 mg, 83 μmol) were successively added at −10°C; the mixture was stirred for 1 h at this temperature and for 18 h at rt before addition of an aqueous saturated NH_4Cl solution (0.5 mL).

4.7.1. 2-(2-Pyridinyl)quinoline (8a). The general procedure 6, using 2-bromopyridine (0.16 mL), gave 28% of **8a** (eluent: CH_2Cl_2): mp 98°C (lit.[33a] 98–99°C); the ^{1}H NMR data are in accordance with those of the literature;[33a] ^{13}C NMR ($CDCl_3$) δ 119.6 (C$_3$), 120.5 (C$_{5'}$), 122.4 (C$_{3'}$), 124.9 (C$_b$), 126.3 (C$_6$), 127.6 (C$_5$), 129.1 (C$_7$), 129.2 (C$_8$), 126.9 (C$_{4'}$), 140.9 (C$_4$), 148.3 (C$_a$), 150.0 (C$_{6'}$), 157.4 (C$_{2'}$), 157.6 (C$_2$); IR (KBr) ν 3050, 3000, 1610, 1595, 1480, 1452, 1324, 1292, 1242, 1091, 1039, 782, 625 cm^{-1}. Anal. calcd for $C_{14}H_{10}N_2$ (206.25): C, 81.53; H, 4.89; N, 13.58. Found: C, 81.34; H, 4.76; N, 13.87%.

4.7.2. 2,2′-Biquinoline (8b). The general procedure 6, using 2-bromoquinoline (**3**, 0.35 g), gave 27% of **8b** (eluent: CH_2Cl_2/Et_2O 80:20). The physical and spectral data are analogous to those obtained for a commercial sample (Fluka).

4.8. General procedure 7: 4-substituted quinolines 9a–b,d by bromine–magnesium exchange of 4 and subsequent cross-coupling with bromides

To THF (4 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, a solution of 4-bromoquinoline (**4**, 0.35 g, 1.7 mmol) in THF (2 mL) was introduced at −30°C, and the mixture was stirred at −10°C for 2 h. A solution of the bromide (1.7 mmol) in THF (3 mL), $Pd(dba)_2$ (48 mg, 83 μmol) and dppf (47 mg, 83 μmol) were successively added at −10°C; the mixture was stirred for 1 h at this temperature and for 18 h at rt before addition of an aqueous saturated NH_4Cl solution (0.5 mL).

4.8.1. 4-(2-Pyridinyl)quinoline (9a). The general procedure 7, using 2-bromopyridine (0.16 mL), gave 43% of **9a** (eluent: CH_2Cl_2/AcOEt 80:20): mp 66°C; ^1H NMR ($CDCl_3$) δ 7.40 (m, 4H, $H_{5,7,3',5'}$), 7.66 (m, 1H, H_6), 7.79 (t, 1H, J=7.6 Hz, $H_{4'}$), 8.05 (d, 1H, J=4.4 Hz, H_3), 8.11 (d, 1H, J=8.5 Hz, H_8), 8.74 (d, 1H, J=4.3 Hz, $H_{6'}$), 8.92 (d, 1H, J=4.4 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 119.4 (C_3), 121.8 ($C_{5'}$), 123.6 ($C_{3'}$), 125.3 (C_6), 125.9 (C_b), 127.5 (C_5), 129.9 (C_7), 130.2 (C_8), 137.2 ($C_{4'}$), 146.9 (C_4), 148.6 (C_a), 149.1 ($C_{6'}$), 150.3 (C_2), 157.4 ($C_{2'}$); IR (KBr) ν 3048, 2997, 1650, 1598, 1367, 1294, 1237, 1101, 786, 623 cm^{-1}. Anal. calcd for $C_{14}H_{10}N_2$ (206.25): C, 81.53; H, 4.89; N, 13.58. Found: C, 81.34; H, 4.61; N, 13.46%.

4.8.2. 4-(5-Bromo-2-pyridinyl)quinoline (9b). The general procedure 7, using 2,5-dibromopyridine (0.40 g), gave 48% of **9b** (eluent: CH_2Cl_2/Et_2O 80:20): mp 126°C; ^1H NMR ($CDCl_3$) δ 7.42 (d, 1H, J=4.4 Hz, H_3), 7.50 (m, 2H, $H_{7,3'}$), 7.68 (m, 1H, H_6), 7.95 (dd, 1H, J=8.3, 2.1 Hz, $H_{4'}$), 8.02 (d, 1H, J=7.7 Hz, H_5), 8.12 (d, 1H, J=8.3 Hz, H_8), 8.82 (d, 1H, J=2.1 Hz, $H_{6'}$), 8.93 (d, 1H, J=4.4 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 121.1 ($C_{5'}$), 121.7 (C_3), 125.7 ($C_{3'}$), 126.1 (C_6), 126.4 (C_b), 127.7 (C_5), 130.0 (C_8), 130.4 (C_7), 139.9 ($C_{4'}$), 145.3 (C_4), 149.3 (C_a), 150.4 (C_2), 151.4 ($C_{6'}$), 155.4 ($C_{2'}$); IR (KBr) ν 3068, 2937, 1583, 1494, 936, 621 cm^{-1}. Anal. calcd for $C_{14}H_9BrN_2$ (285.15): C, 58.97; H, 3.18; N, 9.82. Found: C, 58.76; H, 3.44; N, 9.57%.

4.8.3. 4-(2-Pyrazinyl)quinoline (9d). The general procedure 7, using 2-bromopyrazine (0.27 g), gave 23% of **9d** (eluent: CH_2Cl_2/Et_2O 80:20): mp <50°C; ^1H NMR ($CDCl_3$) δ 7.51 (d, 1H, J=4.5 Hz, H_3), 7.56 (d, 1H, J=7.5 Hz, H_5), 7.74 (t, 1H, J=7.5 Hz, H_6), 8.06 (t, 1H, J=8.5 Hz, H_7), 8.18 (d, 1H, J=8.5 Hz, H_8), 8.66 (d, 1H, J=1.8 Hz, $H_{6'}$), 8.76 (d, 1H, J=1.8 Hz, $H_{5'}$), 8.89 (s, 1H, $H_{3'}$), 9.01 (d, 1H, J=4.5 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 119.3 (C_3), 126.3 (C_6), 126.5 (C_b), 127.6 (C_5), 129.2 (C_8), 129.2 (C_7), 141.8 ($C_{5'}$), 143.7 (C_4), 145.1 ($C_{6'}$), 148.6 (C_a), 150.2 (C_2), 152.5 ($C_{2'}$); IR (KBr) ν 2899, 1643, 1543, 1249, 864, 743, 678 cm^{-1}. Anal. calcd for $C_{13}H_9N_3$ (207.24): C, 75.35; H, 4.38; N, 20.28. Found: C, 75.08; H, 4.34; N, 19.98%.

4.9. 2,3′-Bipyridine (10)

To THF (4 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, 3-bromopyridine (0.16 mL, 1.7 mmol) was introduced at −30°C, and the mixture was stirred at −10°C for 2 h. A solution of 2-bromopyridine (0.16 mL, 1.7 mmol) in THF (3 mL), $Pd(dba)_2$ (48 mg, 83 μmol) and dppf (47 mg, 83 μmol) were successively added at −10°C; the mixture was stirred for 1 h at this temperature and for 18 h at rt before addition of an aqueous saturated NH_4Cl solution (0.5 mL) to afford 62% of **10** (eluent: CH_2Cl_2/Et_2O 50:50, and then MeOH/AcOEt 50:50). The physical and spectral data are analogous to those obtained for a commercial sample (Acros).

4.10. 1-Phenylisoquinoline (11)

To THF (4 mL) at −10°C were added BuMgCl (0.63 mmol) and BuLi (1.3 mmol). After 1 h at −10°C, bromobenzene (0.26 g, 1.7 mmol) was introduced at −30°C, and the mixture was stirred at −10°C for 2.5 h. A solution of 1-bromoisoquinoline (0.35 g, 1.7 mmol) in THF (3 mL), $Pd(dba)_2$ (48 mg, 83 μmol) and dppf (47 mg, 83 μmol) were successively added at −10°C; the mixture was stirred for 1 h at this temperature and for 18 h at rt before addition of an aqueous saturated NH_4Cl solution (0.5 mL) to afford 24% of **11** (eluent: CH_2Cl_2/AcOEt 90:10): mp 85°C (lit.[27b] 88–89°C); the spectral data are in accordance with those of the literature.[27b]

4.11. IR spectroscopic analyses

Samples were recorded using a ReactIR™ 4000 from ASI Applied Systems fitted with an immersible DiComp ATR probe optimized for maximum sensitivity. The spectra were acquired in 64 scans per spectrum at a gain of 1 and a resolution of 8 using system ReactIR™ 2.21 software. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical adjustable-volume ReactIR™ microcell[46] fitted with magnetic stir bar under N_2 atmosphere. Following the recording of a background spectrum (1024 scans), the flask was charged with BuMgCl. IR spectra were collected at 2 min intervals over the course of the reaction. BuLi was added at −75°C, and the temperature was slowly raised to −10°C. 3-Bromoquinoline was then introduced at −60°C, and the temperature was slowly raised to rt before addition of PhCHO.

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17. 3-Bromoquinoline (787, 849, 946 and 1077 cm^{-1}) is instantaneously consumed.
18. 3-Quinolinyllithium was prepared from 3-bromoquinoline, using *tert*-butyllithium in Et_2O at −75°C.
19. 3-Quinolinylmagnesium bromide was prepared from the above 3-quinolinyllithium, adding 0.5 equiv. of $MgBr_2$ at −75°C and allowing the mixture to reach 0°C.
20. Bis(3-quinolinyl)magnesium was prepared from the above 3-quinolinyllithium, adding 1.0 equiv. of $MgBr_2$ at −75°C and allowing the mixture to reach 0°C.
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