

Selective and Multiple Functionalization of Pyridines and Alkaloids *via* Mg- and Zn-Organometallic Intermediates

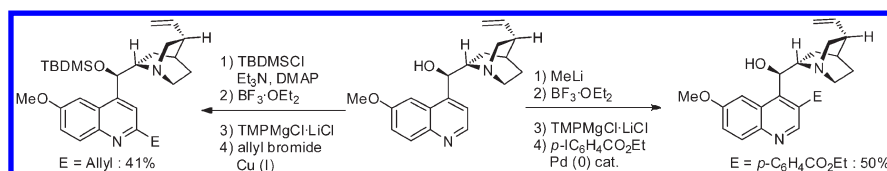
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ABSTRACT



Quinine, nicotine, and related electron-rich amino-substituted pyridines were readily metalated using LiCl-solubilized TMP (2,2,6,6-tetramethylpiperidyl) bases in the presence of BF₃·OEt₂. A full pyridine functionalization of all five positions of the pyridine ring can be realized by using an appropriate combination of TMP bases in the presence or absence of BF₃·OEt₂.

The functionalization of pyridines is an active research field triggered by the diverse biological activities of this class of heterocycles.¹ The preparation of polyfunctional

pyridines can be achieved by ring metalation,² C–H activation,³ or radical functionalization.⁴ Recently, we have found that the combination of the hindered base TMPMgCl·LiCl⁵ (1) with BF₃·OEt₂ allows the regioselective metalation of various electron-poor pyridines.⁶ The metalation of electron-rich substituted pyridines, bearing amino groups, or in general the metalation of alkaloids is of great importance due to their pharmaceutical properties.⁷ The use of BF₃·OEt₂ for the activation of such basic substrates may be complicated by competitive BF₃ complexation to the amino substituents.⁸ Herein, we report the selective metalation of various amino-substituted pyridines, including important alkaloids such as nicotine and quinine. Also, we report successive metalation of the pyridine scaffold, allowing a full ring functionalization.

Thus, the reaction of 4-dimethylaminopyridine (**2a**; DMAP)⁹ with BF₃·OEt₂ (1.1 equiv, THF, 0 °C, 15 min)

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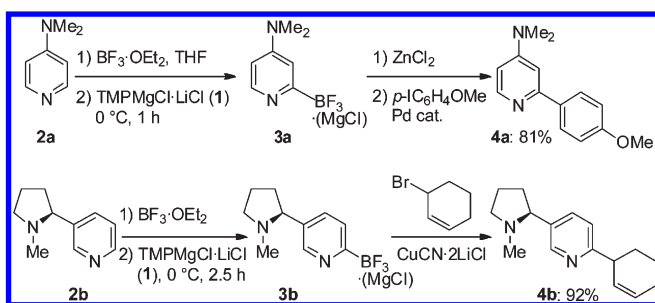
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Scheme 1. Selective Functionalization of **2a** and **2b** Using a Two-Step Metalation Protocol



followed by the addition of $\text{TMPMgCl} \cdot \text{LiCl}$ (**1**; 1.1 equiv, 0 °C, 1 h) furnishes the 2-pyridyltrifluoroborate¹⁰ intermediate **3a**, which after transmetalation with ZnCl_2 ¹¹ and $\text{Pd}(0)$ -catalyzed cross-coupling¹² using $\text{Pd}(\text{dba})_2$ and $\text{P}(2\text{-furyl})_3$ ¹³ with 4-iodoanisole, leads to the 2-arylated DMAP (**4a**) in 81% yield (Scheme 1). In the absence of $\text{BF}_3 \cdot \text{OEt}_2$, the metalation of **2a** with $\text{TMPMgCl} \cdot \text{LiCl}$ (**1**) leads mostly to decomposition. Similarly, the reaction of the trifluoroborate **3a** with other electrophiles such as iodine, 1,1,2-trichloro-1,2,2-trifluoroethane, and an acyl chloride (after $\text{CuCN} \cdot 2\text{LiCl}$ ¹⁴ transmetalation) gives the expected products (**4c–e**) in 68–72% yield (entries 1–3 of Table 1). The 2-chloro-DMAP derivative (**4d**) can be further metalated at position 6 using the same conditions ((i) $\text{BF}_3 \cdot \text{OEt}_2$, 0 °C; (ii) $\text{TMPMgCl} \cdot \text{LiCl}$ (**1**; 1.5 equiv, 0 °C, 3 h)) and provides after iodolysis or copper-mediated allylation the 2,6-functionalized DMAP derivatives (**4g–h**) in 78–80% yield (entries 5 and 6). A sterically hindered 4-aminopyridine derivative such as **2c** bearing a tetramethylpiperidyl moiety at position 4 is metalated under the same conditions. Allylation with ethyl 2-(bromomethyl)acrylate¹⁵ gives the 2-allylated pyridine (**4f**) in 71% yield. Whereas nicotine was previously metalated with various lithium amide^{16,17} or TMP-zincate¹⁶ bases in a nonselective manner, we have found that (*S*)-nicotine (**2b**) can be selectively metalated under mild conditions using our procedure. Thus, the treatment of (*S*)-nicotine (**2b**) with $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 equiv, 0 °C, 15 min) followed by the addition of

$\text{TMPMgCl} \cdot \text{LiCl}$ (**1**; 1.5 equiv, 0 °C, 2.5 h) leads to a selective metalation at position 6. After transmetalation with $\text{CuCN} \cdot 2\text{LiCl}$ (1.1 equiv) and addition of 3-bromocyclohexene (0.8 equiv), the allylated nicotine derivative (**4b**) is obtained in 92% yield (Scheme 1).

Table 1. Selective Metalation of Amino-Substituted *N*-Heterocycles

entry	substrate	electrophile	product, yield % ^a
1		I_2	 4c : 72
2		$\text{Cl}_2\text{FC}-\text{CF}_2\text{Cl}$	 4d : 70
3			 4e : 68 ^b
4			 4f : 71 ^b
5		I_2	 4g : 80
6			 4h : 78 ^b

^a Isolated, analytically pure product. ^b Obtained after transmetalation with $\text{CuCN} \cdot 2\text{LiCl}$ (1.1 equiv).

The functionalization of quinine¹⁸ was pioneered by Hintermann, Gaunt, Ley, and Baran using either radical or nucleophilic additions.^{4c,19} Our metalation protocol was readily applied to this more complex scaffold and allows for the first time to metalate at either position 2 or 3 of the quinoline ring selectively. Thus, the successive treatment of quinine (**5**) with MeLi (1 equiv, 0 to 25 °C, 1 h) and $\text{BF}_3 \cdot \text{OEt}_2$ (2.2 equiv, 0 °C, 15 min) in THF followed by the addition of $\text{TMPMgCl} \cdot \text{LiCl}$ (**1**; 1.1 equiv, 0 °C, 40 min) leads to a specific metalation at position 3 of the quinoline ring triggered by a chelation with the tertiary amine. Quenching with various electrophiles, such as iodine, 1,2-dibromo-1,1,2,2-tetrachloroethane, allyl bromide, and ethyl 4-iodobenzoate in the presence of the appropriate catalyst, produces the 3-substituted quinine derivatives

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(10) The nature of the intermediate organometallic produced after metalation has been established by ¹³C and ¹¹B NMR spectroscopy (ref 6).

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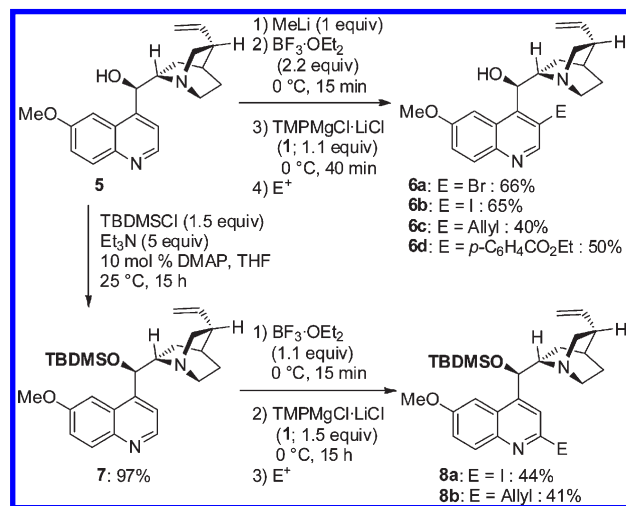
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(**6a–d**) in 40–66% yield (Scheme 2). By increasing the steric bulk near the quinuclidine nitrogen *via* the formation of TBDMS-ether **7** (97% yield),²⁰ it was possible to shift the metalation from position 3 to position 2 of the quino-line ring. Thus, the two-step metalation of **7**, with $\text{BF}_3 \cdot \text{OEt}_2$ /TMPMgCl·LiCl (**1**, 1.5 equiv, 0 °C, 15 h), produces, after quenching with iodine or copper-catalyzed allylation, the 2-substituted quinines **8a** and **8b** in 41–44% yield (Scheme 2).

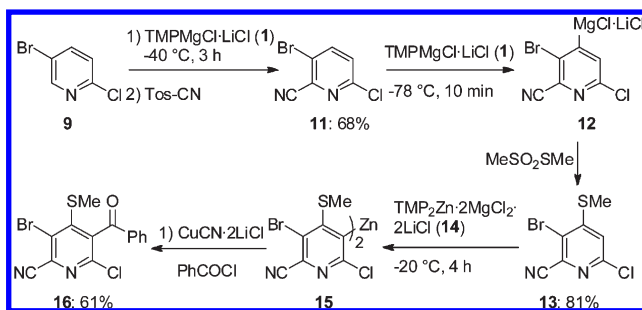
Scheme 2. Functionalization of Quinine (**5**) either at C3 or at C2 Position



To demonstrate further the broad range of applications of this pyridine metalation with an appropriate choice of TMP-bases in the presence (or absence) of $\text{BF}_3 \cdot \text{OEt}_2$, we have performed two full functionalization sequences of the pyridine scaffold starting first with the 2,5-dihalopyridine **9** and with isonicotinonitrile (**10**) (Schemes 3 and 4). Thus, pyridine **9** was first treated with TMPMgCl·LiCl (**1**, 1.1 equiv, –40 °C, 3 h) leading to a regioselective metalation at position 6.

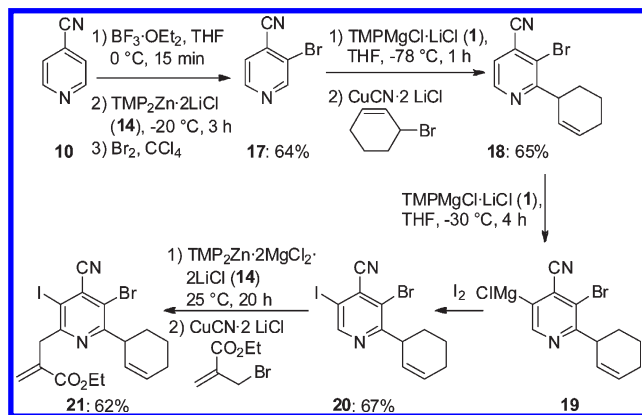
Quenching with tosyl cyanide results in the formation of the 2,3,6-trisubstituted pyridine **11** in 68% yield. Subsequent metalation with **1** (1.1 equiv, –78 °C, 10 min) achieves a further magnesiation at position 4, leading to the functionalized Grignard reagent **12**. Its thiomethylation with MeSO_2SMe provides the 2,3,4,6-tetrasubstituted pyridine **13** in 81% yield. Whereas TMPMgCl·LiCl (**1**) is incompatible with such sensitive pyridines, $\text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}^{21}$ (**14**) smoothly zincates the pyridine **13** at position 5, leading to the *bis*-pyridylzinc reagent **15**. The copper-mediated acylation with PhCOCl leads to the fully substituted pyridine **16** in 61% yield (Scheme 3).

Scheme 3. Full functionalization of the Pyridine Core Starting from the 2,5-Dihalopyridine (**9**)



The full functionalization of a 4-substituted pyridine such as **10** proceeds best by a $\text{BF}_3 \cdot \text{OEt}_2$ -assisted zincation using $\text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ (**14**; 0.55 equiv, –20 °C, 3 h) leading after bromination (Br_2 , 1.1 equiv, –20 to 25 °C) to the 3,4-disubstituted pyridine **17**. The regioselectivity of the metalation may be explained by assuming that BF_3 coordinates at the N-heterocycle and disfavors for steric reasons a metalation at position 2, but the BF_3 activation acidifies all positions and allows a fast metalation at position 3. Also the cyano group directs by its inductive effect the metalation in position 3 or 4. Further magnesiation of **17** with TMPMgCl·LiCl (**1**, 1.1 equiv, –78 °C, 1 h) and a copper-catalyzed allylation with 3-bromocyclohexene give the 2,3,4-trisubstituted pyridine **18** in 65% yield. Repeated magnesiation with TMPMgCl·LiCl (**1**; 1.1 equiv, –30 °C, 4 h) readily generates the Grignard reagent **19**, which after iodolysis provides the tetrasubstituted pyridine **20** in 67% yield. The final functionalization is achieved by treatment of **20** with the mild zinc base $\text{TMP}_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}^{21}$ (**14**; 1.1 equiv, 25 °C, 20 h) giving after a copper-catalyzed allylation the fully substituted pyridine **21** in 62% yield (Scheme 4).

Scheme 4. Full Functionalization of the Pyridine Core Starting from the 4-Substituted Pyridine (**10**)



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In summary, we have demonstrated that TMP bases in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ are versatile reagents for the

functionalization of amino-substituted pyridines and alkaloids. Furthermore, the functionalization of quinine (**5**) at position 2 or 3 was demonstrated as well as the possibility of fully functionalizing pyridines *via* successive metalations using TMP bases in the presence or absence of $\text{BF}_3 \cdot \text{OEt}_2$. Further extensions of this work toward the synthesis of functionalized alkaloids are underway in our laboratories.

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