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

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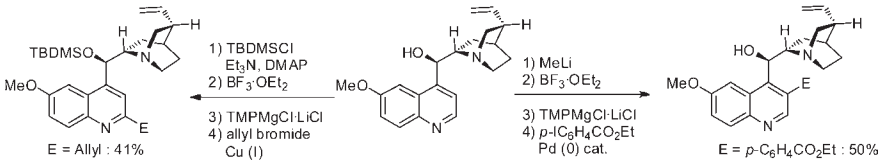
ABSTRACT



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 $BF_3 \cdot OEt_2$. 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 $BF_3 \cdot OEt_2$.

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·LiCl[5] (**1**) with $BF_3 \cdot OEt_2$ 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 $BF_3 \cdot OEt_2$ for the activation of such basic substrates may be complicated by competitive BF_3 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 $BF_3 \cdot OEt_2$ (1.1 equiv, THF, 0 °C, 15 min)

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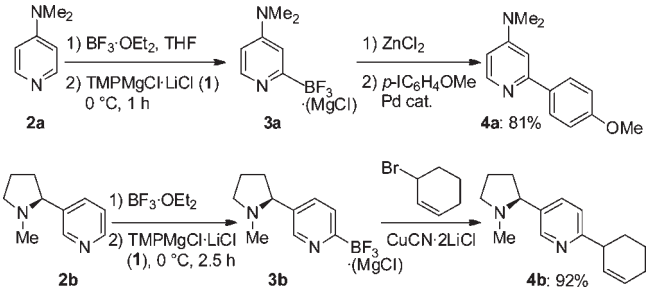
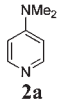
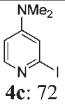
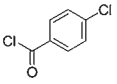
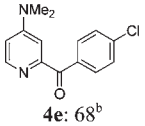
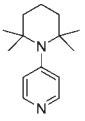
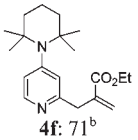
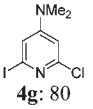
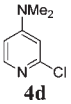
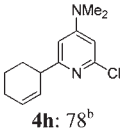
Scheme 1. Selective Functionalization of **2a** and **2b** Using a Two-Step Metalation Protocol



followed by the addition of TMPMgCl·LiCl (**1**; 1.1 equiv, 0 °C, 1 h) furnishes the 2-pyridyltrifluoroborate[10] intermediate **3a**, which after transmetalation with $ZnCl_2$[11] and Pd(0)-catalyzed cross-coupling[12] using $Pd(dba)_2$ and P(2-furyl)$_3$[13] with 4-iodoanisole, leads to the 2-arylated DMAP (**4a**) in 81% yield (Scheme 1). In the absence of $BF_3 \cdot OEt_2$, the metalation of **2a** with TMPMgCl·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 CuCN·2LiCl[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) $BF_3 \cdot OEt_2$, 0 °C; (ii) TMPMgCl·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)acrylate[15] gives the 2-allylated pyridine (**4f**) in 71% yield. Whereas nicotine was previously metalated with various lithium amide[16,17] or TMP-zincate[16] 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 $BF_3 \cdot OEt_2$ (1.1 equiv, 0 °C, 15 min) followed by the addition of TMPMgCl·LiCl (**1**; 1.5 equiv, 0 °C, 2.5 h) leads to a selective metalation at position 6. After transmetalation with CuCN·2LiCl (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	 **2a**	I_2	 **4c**: 72
2	 **2a**	$Cl_2FC\text{-}CF_2Cl$	 **4d**: 70
3	 **2a**		 **4e**: 68[b]
4	 **2c**		 **4f**: 71[b]
5	 **4d**	I_2	 **4g**: 80
6	 **4d**		 **4h**: 78[b]

[a] Isolated, analytically pure product. [b] Obtained after transmetalation with CuCN·2LiCl (1.1 equiv).

The functionalization of quinine[18] 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 $BF_3 \cdot OEt_2$ (2.2 equiv, 0 °C, 15 min) in THF followed by the addition of TMPMgCl·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 ^{13}C and ^{11}B NMR spectroscopy (ref 6).

(11) Without a transmetalation with $ZnCl_2$, the cross-coupling proceeds in lower yields.

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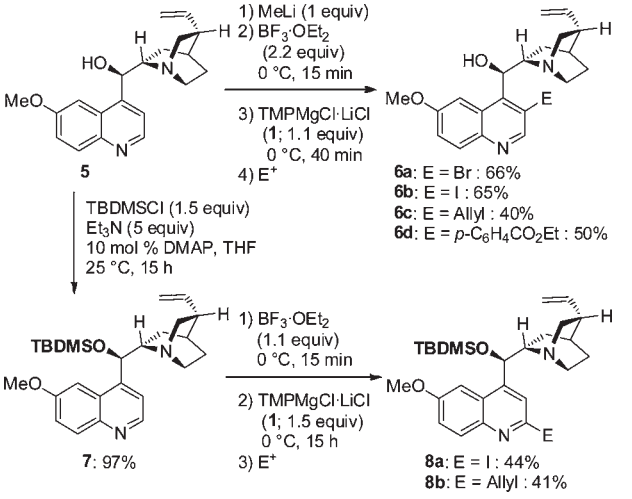
(**6a**–**d**) in 40–66% yield (Scheme 2). By increasing the steric bulk near the quinuclidine nitrogen *via* the formation of TBDMS-ether **7** (97% yield),[20] it was possible to shift the metalation from position 3 to position 2 of the quinoline ring. Thus, the two-step metalation of **7**, with $BF_3 \cdot OEt_2$/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).

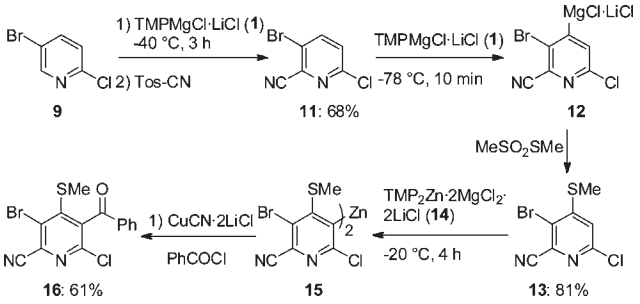
Scheme 2. Functionalization of Quinine (**5**) either at C3 or at C2 Position



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 $BF_3 \cdot OEt_2$, 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 regiospecific metalation at position 6.

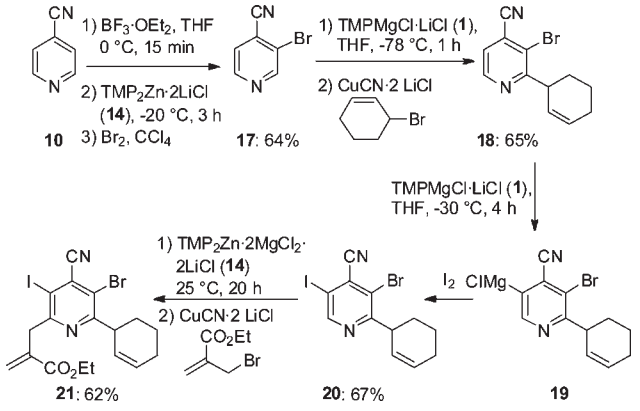
Quenching with tosyl cyanide results in the formation of the 2,3,6-trisubstituted pyridine **11** in 68% yield. Subsequent metalation with **1** (1.1 equiv, −78 °C, 10 min) achieves a further magnesiation at position 4, leading to the functionalized Grignard reagent **12**. Its thiomethylation with $MeSO_2SMe$ provides the 2,3,4,6-tetrasubstituted pyridine **13** in 81% yield. Whereas TMPMgCl·LiCl (**1**) is incompatible with such sensitive pyridines, $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[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 $BF_3 \cdot OEt_2$-assisted zincation using $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**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 $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[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**)



In summary, we have demonstrated that TMP bases in the presence of $BF_3 \cdot OEt_2$ are versatile reagents for the

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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 $BF_3 \cdot OEt_2$. 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.