

# Chichibabin-Type Direct Alkylation of Pyridyl Alcohols with Alkyl Lithium Reagents

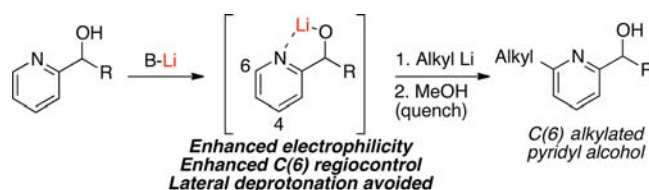
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## ABSTRACT



Direct C(6) alkylation of pyridyl alcohols can be achieved following an initial deprotonation of the hydroxy group. This transformation, which is believed to occur by a Chichibabin-type alkylation, avoids lateral deprotonation prior to pyridine ring alkylation and gives increased regioselectivity for C(6) over C(4) alkylation.

The pyridine heterocycle has emerged as an important structural motif in complex natural products,<sup>1a–c</sup> pharmaceuticals,<sup>1d,e</sup> and designer ligands for catalysis.<sup>2</sup> The efficient preparation and study of pyridine-containing molecules depends on general and direct methods for the functionalization of pyridines and their corresponding picoline derivatives. Not surprisingly, numerous approaches have been established for the direct C(2) and C(6) functionalization of the pyridine nucleus,<sup>3</sup> which include

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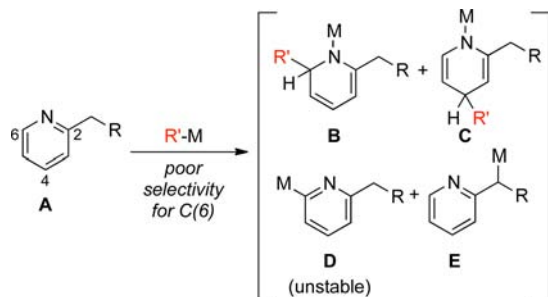
the introduction of heteroatoms (e.g., the Chichibabin reaction),<sup>4</sup> as well as the installation of halogens and carbon substituents (e.g., using deprotonation/functionalization or the Minisci process).<sup>5,6</sup> However, several unmet challenges are inherent in the direct C(6) functionalization of *picoline derivatives* (e.g., **A**, Figure 1).<sup>7</sup> These challenges include competing functionalization at C(4) (e.g., via **C**), as well as lateral functionalization of the picoline group. This latter competing process, which may be initiated by deprotonation of the pseudobenzyl position (see **E**),<sup>7g,h</sup> plagues many attempts to directly functionalize picoline

(5) A recent review: Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642–2713.

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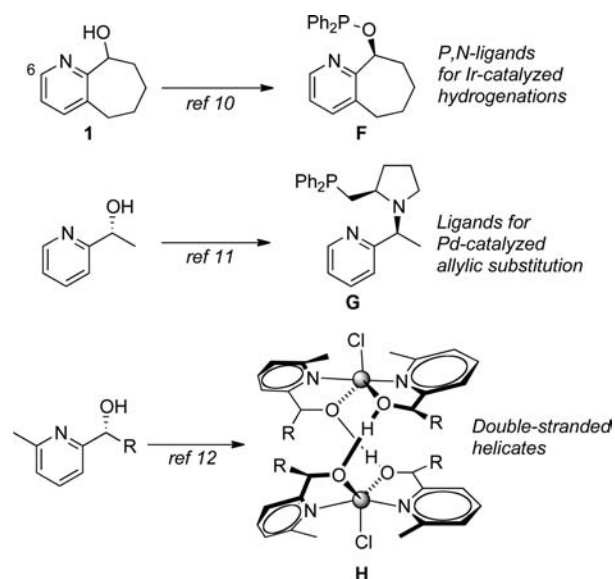
derivatives. In many cases, competing deprotonation leads to a lack of productive reactivity (e.g., via **E**) or decomposition (e.g., via **D**).<sup>7a,e,f</sup>



**Figure 1.** Challenges with direct C(6) functionalization of picoline derivatives by alkyl nucleophile addition.

Recently, a series of metal-mediated approaches to achieve C(6) functionalization of picolines has been introduced, which addresses many of the functional group and regioselectivity challenges inherent in traditional methodologies for pyridine functionalization.<sup>8,9</sup> However, the direct C(6) alkylation of hydroxylated variants of picoline derivatives (pyridyl alcohols) remains unsolved. In this manuscript, we describe a solution to this challenge that relies on a Chichibabin-type alkylation.

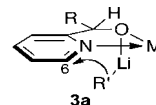
Pyridyl alcohols (e.g., **1**, Figure 2) represent a unique class of picoline derivatives, which has proven broadly useful in the synthesis of ligands for the enantioselective hydrogenation of unactivated olefins (e.g., **F**, Figure 2)<sup>10</sup> or for Pd-catalyzed allylic substitution reactions (e.g., **G**).<sup>11</sup> Additionally, pyridyl alcohols have been found to self-assemble in the presence of certain metal salts to form double-stranded helicates (e.g., **H**).<sup>12</sup> As such, methods that provide direct access to alkylated variants of pyridyl alcohols would be highly valuable. An attractive option to achieve the direct alkylation of pyridyl alcohols would be to employ an alkylative variant of the Chichibabin reaction, which has been previously used in the direct alkylation of pyridines.<sup>7</sup>



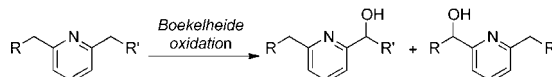
**Figure 2.** Examples of pyridyl alcohol utility.

For example, during investigations on the reactivity of indolizinones,<sup>13</sup> we required efficient access to an alkylated variant of pyridyl alcohol **1** (Figure 2). After extensively investigating various methods for the introduction of a butyl group at C(6) of **1**, it was determined that only the direct, Chichibabin-type reaction with *n*-BuLi furnished the desired product. We postulated that pyridyl alcohols could offer a general solution to the traditional challenges associated with an alkylative Chichibabin-type process. First, by deprotonation of the alcohol group (e.g., in **2**, Scheme 1) with an appropriate base, an alkoxide intermediate would be formed (see **3**), which would be slow to undergo lateral deprotonation (e.g., upon treatment with an alkyl lithium reagent). Second, a potential interaction between the alkoxide counteranion (M) and the pyridine nitrogen of **3** would enhance the electrophilicity at C(6) and also increase the basicity of the alkoxide lone pairs. This potential increase in basicity of the alkoxide was expected to enhance interactions with organometals (see **3a**), which would in turn increase the nucleophilicity of the organometallic toward the pyridine nucleus and also direct its delivery to the proximal C(6) position of **3** (in preference

(14) A three-dimensional depiction of **3a** reveals a potential proximity-guided addition of R'Li to C(6).



(15) This method is especially attractive if one considers the alternative Boekelheide oxidation of substrates where R and R' are similar, which is likely to be nonselective:



(8) Nakao, Y. *Synthesis* **2011**, 3209–3219.

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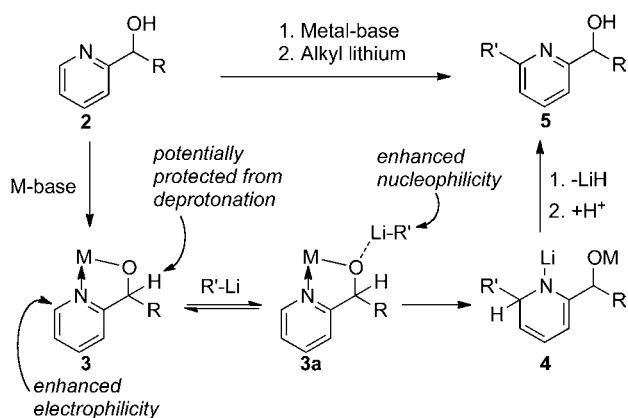
(11) Uenishi, J.; Hamada, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2999–3006.

(12) (a) Telfer, S. G.; Sato, T.; Kuroda, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 581–584. (b) Telfer, S. G.; Kuroda, R. *Chem.—Eur. J.* **2005**, *11*, 57–68.

(13) Hardin Narayan, A. R.; Sarpong, R. *Org. Biomol. Chem.* **2012**, *10*, 70–78.

to C(4)).<sup>14</sup> Finally, loss of LiH and protonation would provide the desired C(6)-alkylated pyridyl alcohol (**5**).<sup>15</sup>

**Scheme 1.** Proposed Facilitation of Chichibabin-Type Alkylation of Pyridyl Alcohols (**2**)



To test this hypothesis, we initiated our studies on the direct alkylation of pyridyl alcohols with **1** (see Table 1), which was prepared from commercially available 2,3-cycloheptenopyridine using a Boekelheide oxidation sequence.<sup>10a</sup> Pyridyl alcohol **1** was treated sequentially with a range of bases followed by *n*-BuLi as the alkyl nucleophile. Thus, using *n*-BuLi as the base (23 °C, 0.5 h), followed by an additional 1.1 equiv of *n*-BuLi as the nucleophile, and stirring at 23 °C for 44 h resulted in 65% conversion to **6** after quenching (with MeOH) and a standard workup (entry 1). Increasing the temperature to 60 °C (entry 2) led to **6** in essentially the same conversion but in a shorter reaction time period (24 h). Upon heating the reaction mixture to 110 °C (entry 3), conversion to **6** (71%) was also observed, along with some byproducts. Interestingly, employing NaH (entry 4) as the base resulted in only 10% conversion, whereas the use of EtMgBr (entry 5) or *n*-BuMgCl (entry 6) as base did not lead to a productive reaction and resulted in the recovery of the starting material.

The optimal reaction conditions (outlined in Table 1, entry 3) were applied to a range of substrates, as illustrated in Figure 3 (see **7–18**; only products are shown). Notably, in the absence of the hydroxy group, polymerization or decomposition was observed for the majority of substrates (e.g., **7a** or **11a**), suggesting an important role for the hydroxy group.<sup>16</sup> Acyclic pyridyl alcohols gave modest to good isolated yields of the alkylated products (see **7b**; **8–12**). For cyclic pyridyl alcohols, only the seven- and eight-membered ring substrates gave satisfactory yields of the alkylated products (compare **13** to **14–17**). Primary and secondary alkyl lithium reagents were competent nucleophiles (e.g., see **14** and **15**, respectively), whereas tertiary alkyl lithiums (see **16**) and aryl lithium

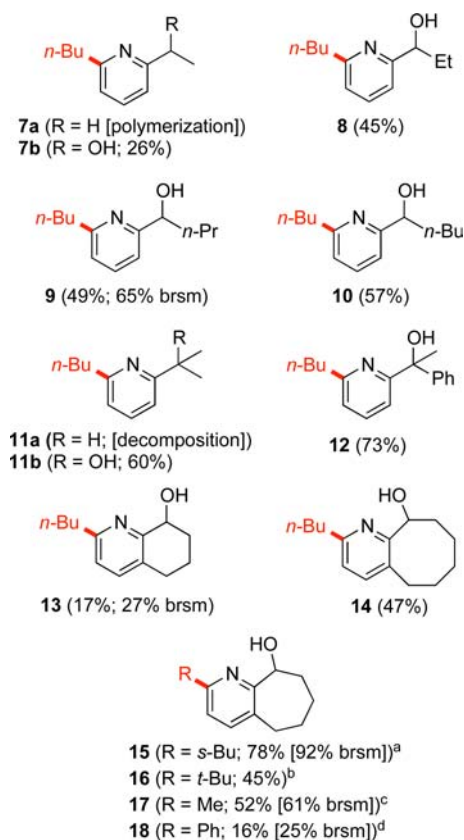
(16) It has been reported (ref 7b, 7c) that, in the presence of an excess of *tert*-butyl lithium, pyridine gives a mixture of alkylated products, including 2,4,6-tri-*tert*-butylpyridine (33% yield in refluxing hexane and 76% yield in refluxing heptane).

nucleophiles (see **18**) led to reduced yields of the adducts (in the latter case, presumably due to competing lithiation of the newly introduced benzene ring).<sup>7b</sup>

**Table 1.** Optimization of the Direct Alkylation of **1**

entry	base	conditions <sup>a</sup>	conversion (%) <sup>b</sup>
1	<i>n</i> -BuLi	23 °C, 44 h	65
2	<i>n</i> -BuLi	60 °C, 24 h	67
3	<i>n</i> -BuLi	110 °C, 24 h	71
4	NaH	110 °C, 24 h	10
5	EtMgBr <sup>c</sup>	110 °C, 24 h	0
6	<i>n</i> -BuMgCl <sup>c</sup>	110 °C, 24 h	0

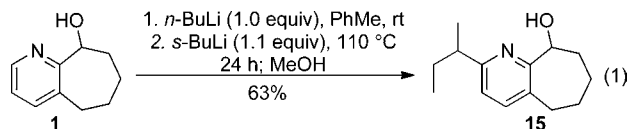
<sup>a</sup> All reactions were performed in PhMe in a Schlenk tube under a N<sub>2</sub> atmosphere. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Alkylmagnesium halides were insoluble under the reaction conditions.



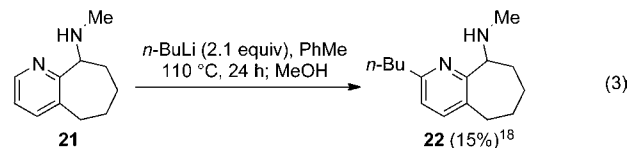
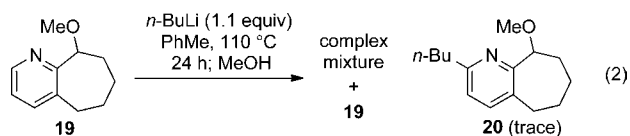
**Figure 3.** Products of the direct alkylation of selected pyridyl alcohols. <sup>a</sup>*s*-BuLi was used as the base. <sup>b</sup>*t*-BuLi was used as the base. <sup>c</sup>MeLi was used as the base. <sup>d</sup>PhLi was used as the base.

To better understand the mechanism and explore the scope of these direct alkylation processes, a series of

experiments, as outlined in eqs 1–4, was undertaken. Pyridyl alcohol **1** was treated with *n*-BuLi (1.0 equiv), followed by *s*-BuLi (1.1 equiv) as the nucleophile. The product, containing an *s*-butyl group at C(6) (**15**, eq 1), was isolated in 63% yield, which suggests that, in principle, only 1.0 equiv of the nucleophile is required. Therefore, for cases where a precious alkyl substituent is required, *n*-BuLi could be employed as the sacrificial base.



When methyl ether **19** (eq 2)<sup>17</sup> was subjected to the alkylation conditions, only a trace amount (2%) of the *n*-butylated product (**20**) was obtained, with the remainder of the mass balance accounted for by unreacted **19** and a complex mixture of unidentified byproducts. This observation suggests that the deprotonation of the hydroxy group is crucial for alkylation. Replacing the oxygen atom of **19** with nitrogen (see methylamine **21**, eq 3) led to a 15% yield of the C(6)-alkylated product (see **22**, eq 3).<sup>18</sup> This observation further emphasizes the seemingly special role of the proximal alkoxide as compared to an amido group.

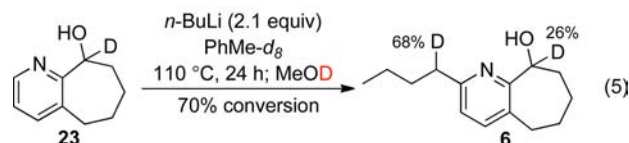
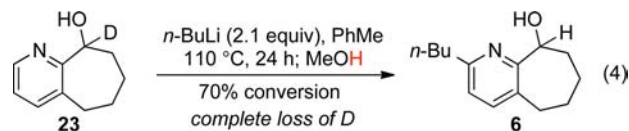


When deuterated substrate **23** (eq 4)<sup>17</sup> was subjected to the alkylation conditions, analysis of the resulting product (i.e., **6**) revealed complete replacement of the pseudo-benzylic deuterium by proton. This result is contrary to our prediction that the carbinol proton is protected from

(17) For details on the preparation of **19**, **21**, and **23**, see the Supporting Information.

(18) The yield was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using 1 mg/mL methenamine as an internal standard.

deprotonation (see **3**, Figure 1). However, the facility of the alkylation reaction (i.e., conversion of **23** to **6**) suggests that deprotonation of the carbinol center, or of the newly introduced pseudo-benzylic position, may occur following alkylation (perhaps by the generated LiH). Support for this hypothesis was obtained by performing the alkylation reaction of **23** in deuterated toluene, followed by quenching with deuterated methanol. Analysis of the resulting product showed the presence of deuterium at both pseudo-benzylic positions of **6**, i.e., at the carbinol center and at the pseudo-benzylic position of the *n*-butyl chain.



In conclusion, the direct alkylation of pyridyl alcohols using alkyl lithium reagents has been accomplished. The reaction is thought to proceed via the intermediacy of a lithium alkoxide intermediate, which enhances the C(6)-alkylation of the pyridine ring. Despite the modest yield of these direct functionalization reactions, they represent an effective one-step alternative to multistep methods that have been previously employed for the synthesis of the target compounds.<sup>10a,c</sup>

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**Supporting Information Available.** Experimental details and copies of <sup>1</sup>H and <sup>13</sup>C spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.