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Directed Deprotonation–Transmetalation as a Route to Substituted Pyridines

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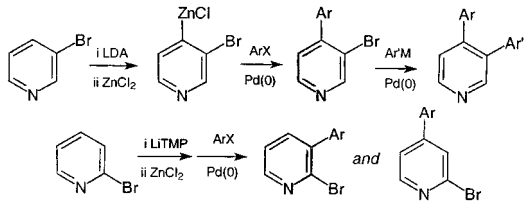
ABSTRACT



Regioselective C-4 deprotonation of 3-bromopyridine, followed by Li/Zn transmetalation and Pd-mediated coupling processes, provides a flexible entry to 4-substituted and 3,4-disubstituted pyridines. Application of a similar sequence to 2-bromopyridine (with LDA as base) provides 2,3-disubstituted pyridines, but using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) provides access to both the 2,3- and 2,4-disubstituted isomers.

Transition metal-mediated cross couplings, based on the reaction of an aryl or alkenyl halide or triflate with an appropriate organometallic component, continue to find important applications in heterocyclic chemistry.[1−3] While such processes have been utilized for the generation of 2- and 3-monosubstituted pyridines, the direct synthesis of 4-substituted variants is frequently hampered by the unstable nature of the 4-halopyridines.[4] Consequently, most approaches have relied on generating a pyridyl-based organometallic component[5] and subsequent coupling of this species with the appropriate aryl or alkenyl halide. Tin,[6] boron,[7] and magnesium[8] 4-pyridyl derivatives have all been reported, and while this strategy is flexible (given the wide range of aryl/alkenyl halides that are also commercially accessible), synthesis of the 4-metallo pyridine component still depends on a halogen−metal exchange reaction that usually involves 4-bromopyridine, an unstable and problematic component.

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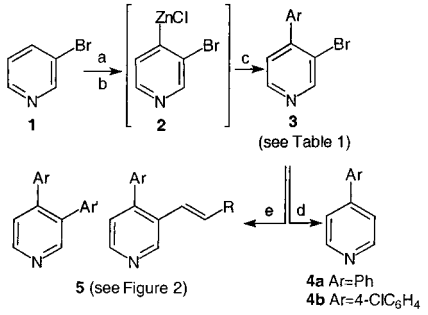
To solve a problem associated with novel nicotinic agonists,[9] we have developed an alternative approach to 4-substituted pyridines that avoids the use of a 4-halopyridine altogether. Instead, directed and regioselective deprotonation and transmetalation (Li → Zn),[10] rather than direct halogen−metal exchange, has been used to provide access to the key organometallic (zinc) component, which is then suitable for a Pd-mediated cross coupling. Importantly, this strategy has a more general application and has been extended to provide a flexible entry to functionalized variants of both 3,4- and 2,3-disubstituted pyridines.

The synthesis of 4-substituted and 3,4-disubstituted pyridines is outlined in Scheme 1 and is based on a one-pot/

Scheme 1. Directed Deprotonation/Transmetalation Route to 4-Substituted and 3,4-Disubstituted Pyridines[a]



[a] Reagents and conditions: (a) LDA, THF, −95 °C; (b) $ZnCl_2$, −95 °C to rt; (c) ArX, $Pd(Ph_3P)_4$, reflux; (d) Rieke zinc, then H_2O; (e) $Ar'B(OH)_2$, $Pd(Ph_3P)_4$, aqueous Na_2CO_3, EtOH, PhMe, *or* $H_2C{=}CHR$, $Pd(OAc)_2$, $(o\text{-Tol})_3P$, NEt_3, MeCN.

three-step sequence: (i) the kinetic *C(4)* lithiation of 3-bromopyridine **1**; (ii) a low-temperature Li−Zn exchange; (iii) Pd(0)-mediated cross coupling of the resulting organozinc intermediate **2** using an aryl or alkenyl halide (or triflate). In this way, 3-bromo-4-substituted pyridines **3** are obtained, which then provide access to both 4-substituted pyridines **4** (following reduction of **3**) and, more significantly, 3,4-disubstituted pyridines **5** via a *second* Pd-mediated cross coupling, based on use of **3** as the aryl halide component.

Deprotonation of 3-bromopyridine **1** was achieved using LDA in THF at −95 °C as reported by Gribble.[11] Addition of $ZnCl_2$ (as a THF solution) was also done at −95 °C, and warming of the solution to room temperature provided the corresponding zinc species **2**.[12] This intermediate, which is stable at room temperature, was then used directly as the 4-pyridyl organometallic component in cross coupling reactions involving aryl and alkenyl halides/triflates. The overall yields for deprotonation, lithium−zinc exchange, and cross coupling were generally good, and the resulting 3-bromo-4-substituted pyridines **3**[13] were isolated following chromatography (Figure 1).

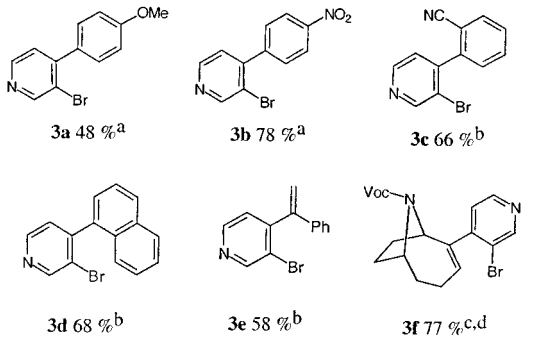


Figure 1. 3-Bromo-4-substituted pyridines. The superscripts a−d denote the following: (a) using the corresponding iodide; (b) using the aryl or alkenyl bromide; (c) using the alkenyl triflate, see ref 9a; (d) Voc = vinyloxycarbonyl.

Interestingly, no "homocoupled" products with **2** acting as both the aryl zinc and aryl bromide fragments were observed; the reactivity associated with the aryl zinc component of **2** appears to dominate. Reduction of **3** (Ar = Ph, 4-ClC_6H_4) using Rieke zinc[14] followed by an aqueous quench then allowed access to the corresponding 4-monosubstituted pyridines **4a** and **4b** in 81% and 64% overall yields, respectively, from 3-bromopyridine, as shown in Scheme 1.

While reduction of **3** to give **4a/b** is straightforward, the reactivity associated with the 3-bromo substituent of **3** can be harnessed in a synthetically more versatile manner,

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providing an entry to 3,4-disubstituted pyridines **5** (Figure 2). This has been illustrated by reaction of **3** in Suzuki

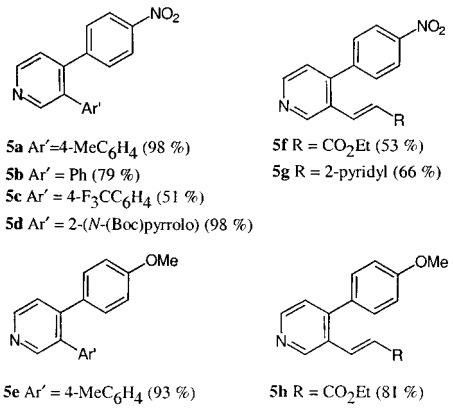
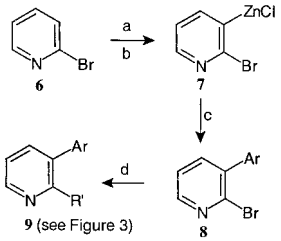


Figure 2. 3,4-Disubstituted pyridines.

couplings (to give **5a**−**e**) and in the Heck reaction (leading to **5f**−**h**).[15]

Directed deprotonation and transmetalation has more general utility and within the pyridine area can also be applied successfully to the synthesis of 2,3-disubstituted derivatives starting from 2-bromopyridine (Scheme 2).

Scheme 2. Directed Deprotonation/Transmetalation Route to 2,3-Disubstituted Pyridines[a]



[a] Reagents and conditions: (a) LDA, THF, −95 °C; (b) $ZnCl_2$, −95 °C to rt; (c) ArX, $Pd(Ph_3P)_4$, reflux; (d) 4-$MeC_6H_4B(OH)_2$, $Pd(Ph_3P)_4$, aqueous Na_2CO_3, EtOH, PhMe, *or* $H_2C{=}CHCO_2Et$, $Pd(OAc)_2$, (*o*-Tol)$_3$P, NEt_3, MeCN.

Using a similar sequence to that described above, deprotonation[11,16] of 2-bromopyridine **6** followed by Li−Zn exchange gave organozinc **7,** and Pd-mediated coupling using aryl iodides then provided a series of 2-bromo-3-substituted pyridines **8a**−**c** in good yields. Again, the 2-bromo moiety of **8a** is amenable to a second Pd-mediated process (either Suzuki or Heck) to afford representative 2,3-disubstituted pyridines **9a** and **9b** (Figure 3).

The interesting issue of the relative kinetic acidity of *C-(4)* vs *C(3)* in 2-bromopyridine **6** has also been examined (Scheme 3). Deprotonation of **6** using LDA (at −95 °C) provides almost exclusively (>95:5) the *C(3)* derivatives **8** (see Scheme 2). However, simply changing the base component and using LiTMP[17] (at −78 °C) rather than LDA provides, after transmetalation ([M] = Li → Zn) and Pd(0) cross coupling, an approximately 3:1 mixture of **8** (major isomer) and the unexpected *C(4)* adduct **10** (minor isomer) (Scheme 3). The ratio of **8** and **10** appears to be established in the initial deprotonation[18] and transmetalation steps, and while there is scope to improve the level of regiocontrol available, this observation provides a basis for a novel but, more importantly, direct entry to 2,4-disubstituted pyridines: adduct **10a** underwent Suzuki coupling to give the 2,4-diarylpyridine **11** in 82% yield.

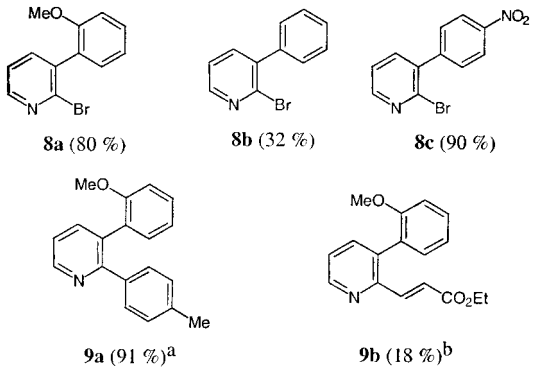
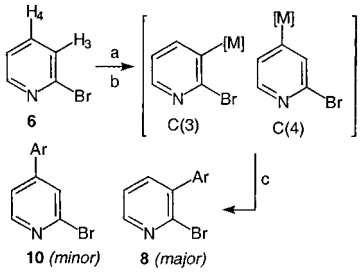
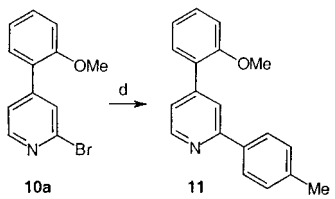


Figure 3. 2,3-Disubstituted pyridines. The superscripts a and b denote the following: (a) yield from **8a**; (b) in this case, the Heck product **9b** was accompanied by 38% of 3-(4-methoxyphenyl)-pyridine and 26% of the product corresponding to reduction of the alkenyl moiety of **9b**.

Scheme 3. C-3 vs C-4 Deprotonation/Transmetalation of 2-Bromopyridine. Synthesis of 2,4-Disubstituted Pyridines[a]



8a/10a Ar = 2-$MeOC_6H_4$ (84 %)
8b/10b Ar = C_6H_5 (39 %)
8c/10c Ar = 4-$NO_2C_6H_4$ (78 %)
8d/10d Ar = 4-$MeOC_6H_4$ (59 %)



[a] Reagents and conditions: (a) LiTMP, THF, −78 °C; (b) $ZnCl_2$, −95 °C to rt; (c) ArX, $Pd(Ph_3P)_4$, reflux; (d) 4-$MeC_6H_4B(OH)_2$, $Pd(Ph_3P)_4$, aqueous Na_2CO_3, EtOH, PhMe (82%).

In summary, exploiting the kinetic acidity associated with 3-bromopyridine provides regioselective access to the corresponding 4-organozinc species **2** via low-temperature *deprotonation* followed by lithium−zinc *transmetalation*. Using similar procedures, 2-bromopyridine provides the corresponding 3-organozinc derivative **7**, and both **2** and **7** undergo facile cross coupling reactions leading to a range of substituted pyridines. It is important to recognize the dual role of the halogen component in **2** and **7**. This moiety not only provides the activation for directing the initial deprotonation step but remains available for further manipulation at a later stage. While a number of intriguing regiochemical issues remain to be fully explored, the ability to combine halogen-directed deprotonation *and* transmetalation provides an effective alternative to direct halogen−metal exchange (to provide simple variants such as **4**) and a versatile entry to variously substituted pyridines.

Acknowledgment. We thank BBSRC for financial support and acknowledge use of the EPSRC's Chemical Database Service at Daresbury.[19]

Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR and other characterization data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For the application of LiTMP to the deprotonation of diazines, see: Mojovic, L.; Turck, A.; Plé, N.; Dorsy, M.; Ndzi, B.; Quéguiner, G. *Tetrahedron* **1996**, *52*, 10417−10426. Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *Tetrahedron* **1998**, *54*, 9701−9710. Turck, A.; Plé, N.; Lepretre-Gaquere, A.; Quéguiner, G. *Heterocycles* **1998**, *49*, 205−214.

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