

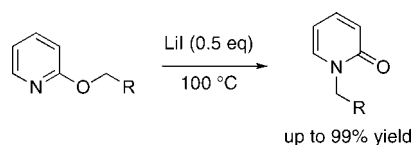
## Synthesis of Substituted *N*-Benzyl Pyridones via an *O*- to *N*-Alkyl Migration

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A new LiI-promoted *O*- to *N*-alkyl migration has been developed for the conversion of *O*-alkylated 2-hydroxy pyridines, quinolines, and pyrimidines to the corresponding *N*-alkylated heterocycles in good to excellent yields (57–99%). This method serves as an efficient means for the preparation of *N*-benzyl pyridones, quinolones, and pyrimidones.

Due to the prominence of *N*-alkylated heterocycles within both natural product<sup>2</sup> and pharmacologically active structures,<sup>3</sup> a selective *N*- versus *O*-alkylation of aromatic imidate systems remains an important synthetic goal. Although intermolecular methods have been explored with varying degrees of success, *O*-alkylation is often a competing process due to the aromatic character of 2-oxypyridine anions.<sup>4</sup> Attempts to improve the selectivity of intermolecular alkylations of 2-pyridone by adding various salts<sup>5</sup> or phase transfer catalysts<sup>6</sup> have shown some

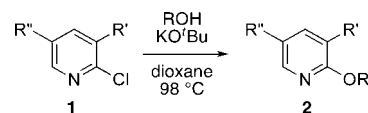
promise; however, the methods remain limited to activated electrophiles and often require specifically substituted pyridones.

In an attempt to develop a more general method, *O*-alkylated pyridines have been explored as a means for accessing *N*-alkylated pyridones. Ikehara and Tanaka first described this type of interconversion within nucleoside motifs in 1974.<sup>7</sup> More recently, Bowman and co-workers demonstrated that 2-methoxy pyridines could be converted into *N*-alkylated pyridones in moderate to good yields in the presence of an activated electrophile and NaI.<sup>8</sup> Both of these methods require the use of a sufficiently nucleophilic heterocycle, as initial alkylation to form a pyridinium salt is required to initiate C–O bond cleavage. Using a similar approach, Ruda and co-workers tethered 2-oxypyridines directly to a solid support through the alkoxy substituent. Upon nitrogen alkylation, cleavage of the desired pyridones from the resin occurred, facilitating their isolation.<sup>9</sup> Although a broader range of electrophiles could be used under these conditions, yields were generally only moderate (19–86%). In a more specialized case, (*N*)-allyl-2-pyridones have been synthesized by treating 2-allyloxy pyridines with a palladium catalyst.<sup>10</sup>

Herein, we report the use of substituted 2-benzyloxy pyridines and other 2-benzyloxy heterocyclic analogues as useful precursors to *N*-benzyl pyridones and related heterocycles. This method allows for the incorporation of a wide range of substituted benzyl groups in high yields with complete consumption of the residual *O*-alkylated material. In addition, this method can be used to prepare *N*-benzyl quinolone and pyrimidone derivatives.

The synthesis of the required 2-alkoxy derivatives **2** was achieved by treating 2-chloropyridine (**1**) (or a substituted derivative) with benzyl or a related alcohol in the presence of potassium *tert*-butoxide (Scheme 1). In this way, a variety of readily available alcohols could be incorporated into 2-alkoxy pyridines in good to excellent yields (Table 1).

### SCHEME 1. Synthesis of 2-Alkoxy pyridines



Initial efforts to convert 2-benzyloxy pyridine (**2a**) into pyridone **3a** focused on the use of various additives at elevated temperature (Scheme 2). Using microwave heating, TFA, BF<sub>3</sub>•OEt<sub>2</sub>, and LiI were each examined as possible catalysts for the transformation (Table 2, entries 1–3). While all three species were found to facilitate the formation of the desired product **3a** at 200 °C in CH<sub>3</sub>CN, benzylacetamide was observed as a byproduct in the presence of either TFA or BF<sub>3</sub>•OEt<sub>2</sub>.<sup>11</sup>

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(7) Ikehara, M.; Tanaka, S. *Tetrahedron Lett.* **1974**, *15*, 497–500.

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(11) Benzylacetamide is presumed to form via a Ritter process, see: (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048.

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(1) Current address: Department of Chemistry, University of Michigan, 930 N. University Ave., Ann Arbor, MI 48109.

(2) Some representative examples, include: (a) Wall, M. E.; Wani, M. C. *J. Ethnopharmacol.* **1996**, *51*, 239–253. Lupin alkaloids: (b) Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419–2423. Cerpegin: (c) Adibatti, N. A.; Thirugnanasambantham, P.; Kulothungan, C.; Viswanathan, S.; Kameswaran, L.; Balakrishna, K.; Sukumar, E. *Phytochemistry* **1991**, *30*, 2449–2450. Map-picine: (d) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215–1217.

(3) Some representative examples, include: (a) Huffman, J. W.; Lu, J.; Hynd, G.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2001**, *9*, 2863–2870. (b) Parlow, J. J.; South, M. S. *Tetrahedron* **2003**, *59*, 7695–7701.

(4) Review: (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757–1779, and references therein.

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TABLE 1. Synthesis of 2-Alkoxyppyridines 2a–q

| entry | R'              | R''             |    |                  |                  |                  | yield (%) <sup>a,b</sup> |    |
|-------|-----------------|-----------------|----|------------------|------------------|------------------|--------------------------|----|
|       |                 |                 | W  | X                | Y                | Z                |                          |    |
| 1     | H               | H               | H  | H                | H                | H                | <b>2a</b>                | 77 |
| 2     | H               | H               | H  | CH <sub>3</sub>  | H                | H                | <b>2b</b>                | 92 |
| 3     | H               | H               | H  | OCH <sub>3</sub> | H                | H                | <b>2c</b>                | 89 |
| 4     | H               | H               | H  | Cl               | H                | H                | <b>2d</b>                | 93 |
| 5     | H               | H               | H  | H                | CH <sub>3</sub>  | H                | <b>2e</b>                | 91 |
| 6     | H               | H               | H  | H                | OCH <sub>3</sub> | H                | <b>2f</b>                | 97 |
| 7     | H               | H               | H  | H                | Cl               | H                | <b>2g</b>                | 94 |
| 8     | H               | H               | H  | H                | H                | CH <sub>3</sub>  | <b>2h</b>                | 84 |
| 9     | H               | H               | H  | H                | H                | OCH <sub>3</sub> | <b>2i</b>                | 87 |
| 10    | H               | H               | H  | H                | H                | Cl               | <b>2j</b>                | 97 |
| 11    | H               | H               | Cl | H                | H                | Cl               | <b>2k</b>                | 99 |
| 12    | H               | CH <sub>3</sub> | H  | H                | H                | H                | <b>2l</b>                | 78 |
| 13    | CH <sub>3</sub> | H               | H  | H                | H                | H                | <b>2m</b>                | 98 |
| 14    | H               | H               |    |                  |                  |                  | <b>2n</b>                | 98 |
| 15    | H               | H               |    |                  |                  |                  | <b>2o</b>                | 89 |
| 16    | H               | H               |    |                  |                  |                  | <b>2p</b>                | 58 |
| 17    | H               | H               |    |                  |                  |                  | <b>2q</b>                | 92 |

<sup>a</sup> Conditions: 2-chloropyridine or a substituted analogue (1.0 equiv), ROH (1.5 equiv), KO<sup>t</sup>Bu (1.5 equiv), 1,4-dioxane (0.22 M), 98 °C, 18 h. <sup>b</sup> Isolated yields.

SCHEME 2. Conditions for the Conversion of 2-Benzyloxyppyridine (2a) into (N)-Benzyl-2-pyridone (3a)

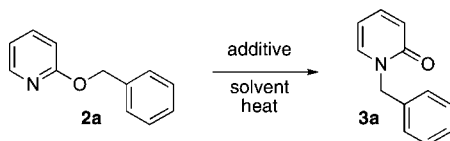


TABLE 2. Conditions for the Conversion of 2-Benzyloxyppyridine (2a) into (N)-Benzyl-2-pyridone (3a)

| entry | additive (equiv)                        | solvent (M)               | temp (°C)        | 2a:3a <sup>a</sup> |
|-------|---|---------------------------|------------------|--------------------|
| 1     | CF <sub>3</sub> COOH (1.0)              | CH <sub>3</sub> CN (0.26) | 200 <sup>b</sup> | 1:5 <sup>c</sup>   |
| 2     | BF <sub>3</sub> ·OEt <sub>2</sub> (0.1) | CH <sub>3</sub> CN (0.26) | 150 <sup>b</sup> | 1.8:1 <sup>c</sup> |
| 3     | LiI (3.0)                               | CH <sub>3</sub> CN (0.26) | 200 <sup>b</sup> | 1:3                |
| 4     | LiI (3.0)                               | CH <sub>3</sub> CN (0.26) | 150 <sup>d</sup> | 2.5:1              |
| 5     | LiI (3.0)                               | CH <sub>3</sub> CN (0.44) | 150 <sup>d</sup> | 0:1                |
| 6     | LiI (1.5)                               | CH <sub>3</sub> CN (0.53) | 150 <sup>d</sup> | 0:1                |
| 7     | LiI (1.5)                               | CH <sub>3</sub> CN (0.53) | 100 <sup>d</sup> | 1:6                |
| 8     | LiI (1.5)                               | neat <sup>e</sup>         | 100 <sup>d</sup> | 0:1                |
| 9     | LiI (0.5)                               | neat <sup>e</sup>         | 100 <sup>d</sup> | 0:1                |
| 10    | LiI (0.25)                              | neat <sup>e</sup>         | 100 <sup>d</sup> | 1:3                |
| 11    | LiI (0.1)                               | neat <sup>e</sup>         | 100 <sup>d</sup> | 3:1                |
| 12    | LiI (0.0)                               | neat <sup>e</sup>         | 100 <sup>d</sup> | 1:0                |
| 13    | LiI (0.5)                               | neat <sup>e</sup>         | rt <sup>f</sup>  | 1:0                |

<sup>a</sup> Determined by either HPLC or <sup>1</sup>H NMR analysis. <sup>b</sup> Microwave heating for 10 min. <sup>c</sup> Benzylacetamide formed as a byproduct. <sup>d</sup> Conventional heating for 26 h. <sup>e</sup> Neat = no solvent. <sup>f</sup> rt = room temperature.

As this byproduct was not observed in the LiI-promoted case, LiI was targeted for further development.

Optimization of the LiI-promoted migration focused on reducing the reaction temperature and the amount of LiI required. Utilizing conventional heating, the efficiency of the reaction improved as the concentration of pyridine **2a** was

SCHEME 3. Optimized Conditions for the Conversion of 2-Alkoxyppyridines into (N)-Alkyl-2-pyridones

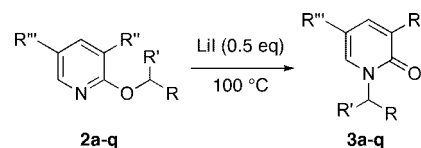


TABLE 3. Conversion of 2-Alkoxyppyridines 2a–q into (N)-Alkyl-2-pyridones 3a–q

| entry | R   | R'              | R''             | R'''            | yield <sup>a,b,c</sup> |                 |
|-------|---|-----------------|-----------------|-----------------|------------------------|-----------------|
|       |   |                 |                 |                 | 8 h                    | 26 h            |
| 1     | C <sub>6</sub> H <sub>5</sub> ( <b>2a</b> )                     | H               | H               | H               | 91                     | 94              |
| 2     | 4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )   | H               | H               | H               | 97                     | 99              |
| 3     | 4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )  | H               | H               | H               | 84                     | 88              |
| 4     | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )                 | H               | H               | H               | 80                     | 90              |
| 5     | 3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )   | H               | H               | H               | 96                     | 91              |
| 6     | 3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )  | H               | H               | H               | 94                     | 96              |
| 7     | 3-ClC <sub>6</sub> H <sub>4</sub> ( <b>2g</b> )                 | H               | H               | H               | 85                     | 93              |
| 8     | 2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )   | H               | H               | H               | 91                     | 97              |
| 9     | 2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ( <b>2i</b> )  | H               | H               | H               | 88                     | 85              |
| 10    | 2-ClC <sub>6</sub> H <sub>4</sub> ( <b>2j</b> )                 | H               | H               | H               | 79                     | 75              |
| 11    | 2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>2k</b> ) | H               | H               | H               | —                      | 72              |
| 12    | 2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>2k</b> ) | H               | H               | H               | 85 <sup>d</sup>        | 88 <sup>d</sup> |
| 13    | 2-naphthyl ( <b>2n</b> )  | H               | H               | H               | 95                     | —               |
| 14    | C <sub>6</sub> H <sub>5</sub> ( <b>2l</b> )                     | H               | H               | CH <sub>3</sub> | 93                     | 93              |
| 15    | C <sub>6</sub> H <sub>5</sub> ( <b>2m</b> )                     | H               | CH <sub>3</sub> | H               | —                      | 57 <sup>d</sup> |
| 16    | C <sub>6</sub> H <sub>5</sub> ( <b>2o</b> )                     | CH <sub>3</sub> | H               | H               | —                      | 34              |
| 17    | CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> ( <b>2p</b> )     | H               | H               | H               | —                      | NR <sup>e</sup> |
| 18    | 3-pyridyl ( <b>2q</b> )   | H               | H               | H               | —                      | NP <sup>f</sup> |

<sup>a</sup> Conditions: substrate (1.0 equiv), LiI (0.5 equiv), 100 °C. <sup>b</sup> Isolated yields. <sup>c</sup> Mean values from duplicate experiments (±3%). <sup>d</sup> 1.0 equiv of LiI used. <sup>e</sup> NR = no reaction, starting material recovered. <sup>f</sup> NP = no product, a number of unidentified byproducts were observed in addition to recovered starting material.

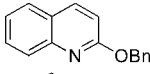
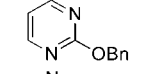
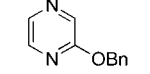
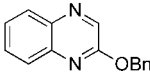
increased (Table 2, entries 4–8). In fact, complete conversion to pyridone **3a** could be achieved at 100 °C if the solvent was removed completely. In addition, using these conditions, a substoichiometric amount of LiI could be used while still achieving complete conversion to pyridone **3a** (entries 8–11). Although some conversion was observed with as little as 0.1 equiv of LiI, 0.5 equiv was found to reliably convert 2-benzyloxyppyridine (**2a**) to the *N*-alkylated derivative **3a** quantitatively after 26 h. Finally, control reactions showed that the migration requires both LiI and heat to occur; only pyridine **2a** was observed after 26 h in the absence of LiI or when the reaction was conducted at room temperature (entries 12 and 13). Considering that 2-pyridones are known to be significantly more stable thermodynamically than their pyridine analogues, the absence of any thermally promoted migration after 26 h at 100 °C is noteworthy.<sup>12,13</sup>

The tolerance of the reaction toward further substitution was next explored using the optimized reaction conditions (Scheme 3). Substituents at any position on the aryl ring were found to have little influence on the efficiency of the transformation (Table 3, entries 1–10). In each case, high yields of the *N*-alkylated product could be isolated after only 8 h. The product, however, remained stable under the reaction conditions and similar or slightly better yields were achieved after 26 h.

(12) Beak, P.; Bonham, J.; Lee, J. T., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1569–1582.

(13) The incomplete thermal rearrangement of alkoxyppyridines to give the corresponding (*N*)-alkyl pyridones using flash vacuum pyrolysis at 600 °C has been observed previously, see: (a) Lister, T.; Prager, R. H.; Tsaconas, M.; Wilkinson, K. L. *Aust. J. Chem.* **2003**, *56*, 913–916.

TABLE 4. Synthesis and Evaluation of Heterocyclic Analogues

| entry | substrate   | synthesis           |                    | migration               |                      |    |
|-------|---|---------------------|--------------------|-------------------------|----------------------|----|
|       |   | method <sup>a</sup> | yield <sup>b</sup> | conditions <sup>c</sup> | yield <sup>b,d</sup> |    |
| 1     |  | 4                   | A                  | 94                      | C                    | 71 |
| 2     |  | 5                   | B                  | 88                      | D                    | 61 |
| 3     |  | 6                   | B                  | 81                      | E                    | 39 |
| 4     |  | 7                   | B                  | 83                      | C                    | 20 |

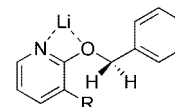
<sup>a</sup> Conditions: A: 2-chloroquinoline (1.0 equiv), benzyl alcohol (1.5 equiv), KO<sup>t</sup>Bu (1.5 equiv), 1,4-dioxane (0.22 M), 98 °C, 18 h. B: 2-chloro-heterocycle (1.0 equiv), benzyl alcohol (1.8 equiv), NaH (1.8 equiv), 1,2-dimethoxyethane, 45 °C, 1 h. <sup>b</sup> Isolated yields. <sup>c</sup> Conditions: C: substrate (1.0 equiv), LiI (1.0 equiv), 110 °C, 26 h. D: substrate (1.0 equiv), LiI (1.0 equiv), 100 °C, 26 h. E: substrate (1.0 equiv), LiI (2.0 equiv), 110 °C, 26 h. <sup>d</sup> Mean values from duplicate experiments (±3%).

Changing the substituent at a given position was found to have only a minimal effect on the isolated yields (entries 1–4, 5–7 and 8–10). Additionally, yields were largely unaffected by increasing steric hindrance at the ortho position (entries 8–10). Even 2-(2,6-dichlorobenzyloxy)pyridine (**2k**) underwent facile alkyl migration, albeit in a slightly reduced 72% yield (entry 11). In this case, simply utilizing a full equivalent of LiI afforded an improved 88% yield of the desired disubstituted product **3k** (entry 12). 2-Naphthylpyridone (**2n**) also underwent efficient conversion under the standard reaction conditions, affording (*N*-naphthyl-2-pyridone (**3n**) in 95% yield after 8 h (entry 13).

In contrast, when regions other than the phenyl ring were altered, the reaction was less robust. Whereas 5-methyl-substituted pyridine **2l** afforded a 93% yield of product **3l**, the 3-methyl substituted pyridine **2m** gave only 57% yield of the desired pyridone **3m** (Table 3, entries 14 and 15). In a similar manner, substituting the benzylic position, as in 2-( $\alpha$ -methylbenzyloxy)pyridine (**2o**), significantly reduced the yield, providing only 34% of the desired product **3o** (entry 16). The inclusion of an additional methylene spacer in alkyl derivative **2p** was even more problematic, inhibiting the reaction completely and affording only recovered starting material (entry 17). Similarly, when pyridine **2q**, containing a 3-pyridyl group, was subjected to the reaction conditions no product was isolated, although in this case, a number of unidentified byproducts were observed in addition to recovered starting material. The failure of the phenethyloxy substituted pyridine **2p** to undergo alkyl migration can be attributed to the less electrophilic nature of the oxygen-bound carbon. In the case of methyl substituted derivatives **2m** and **2o**, the reduction in yield is likely the result of a negative steric interaction imposed by the substituent.

2-Benzyloxy-substituted heterocycles other than pyridine proved to be more challenging systems, both to prepare and in the LiI-promoted migration. While quinoline derivative **4** was synthesized in 94% yield from 2-chloroquinoline using the standard reaction conditions (*tert*-butoxide, 1,4-dioxane, 98 °C), attempts to prepare analogues **5–7** using these conditions met with failure (Table 4). Utilizing a NaH variation of the protocol, however, it was possible to isolate compounds **5–7** in 81–88% yield (entries 2–4).<sup>14</sup>

When the standard migration conditions (0.5 equiv LiI, 100 °C, 26 h) were applied to derivatives **4–7**, little or no



R = H (minimal steric interference)  
R = CH<sub>3</sub> (increased steric interference)

FIGURE 1. One possible coordination mode for the LiI-promoted *O*-to-*N*-alkyl migration.

conversion was observed. Increasing the amount of LiI and the temperature did, however, allow for the transformation of quinoline derivative **4** and pyrimidine analogue **5** to the corresponding *N*-alkylated species in moderate yields (Table 4, entries 1 and 2). In the case of 2-benzyloxyquinoline (**4**), the reaction afforded a 71% yield of (*N*)-benzyl-2-quinolone (**8**) at 110 °C in the presence of a full equivalent of LiI; (*N*)-protio-2-quinolone accounted for the remainder of the mass. While the reaction of 2-benzyloxy-pyrimidine (**5**) produced many more unidentifiable byproducts, it was still possible to isolate (*N*)-benzyl-2-pyridone (**9**) in 61% yield when compound **5** was treated with 1 equivalent of LiI at 100 °C. Unfortunately, the reaction of pyrazine and quinoxaline analogues **6** and **7** produced far greater amounts of unidentifiable byproduct. Under the best conditions, neither *N*-alkylated species could be isolated in greater than 39% yield (entries 3 and 4). As with substrate **2q** (containing a 3-pyridyl group), the inclusion of an additional nitrogen atom away from the alkoxy substituent seems to hinder the desired alkyl migration.

The mechanism of the LiI-promoted conversion of 2-benzyloxy-pyridines into *N*-alkylated pyridones remains an active area of research in our laboratories; however, some details can be gleaned from the experiments reported herein. Unlike the migration observed in the presence of either TFA or BF<sub>3</sub>•OEt<sub>2</sub>, no benzylacetamide was observed when the reaction was promoted by LiI (Table 2, entries 1–3). This observation, in conjunction with the reduced yield in the reaction of pyridine **2o**, which is substituted at the benzylic position, suggests that the reaction does not proceed through a discrete carbocation. Rather, cleavage of the C–O bond likely relies on either a nucleophilic iodide or the nitrogen of another molecule of benzyloxy-pyridine. Such a bimolecular process is further supported by the increased rate of reaction at higher concentrations (Table 2, entries 4–8). In addition, substitution of the pyridine ring at the 3-position, adjacent to the benzyloxy substituent, was shown to reduce the yield of the alkyl migration. This reduction in efficiency would be expected if the approach of an external nucleophile to the benzylic position was disrupted, as might be the case if the lithium were coordinated to both the nitrogen and oxygen atoms of the 2-oxypyridine substrate (Figure 1). The results of further mechanistic investigations will be reported in due course.

In summary, we have developed a new LiI-promoted reaction for converting *O*-alkylated pyridines, quinolines, and pyrimidines into the corresponding *N*-alkylated heterocycles in good to excellent yield (57–99%). Despite some limitations, this transformation provides an excellent means for the preparation of *N*-benzyl pyridones, quinolones, and pyrimidones and should find wide use in synthetic applications.

## Experimental Section

**General Experimental Procedure for the Synthesis of 2-Alkoxy-pyridines. 2-(2-Naphthylpyridone (**2n**).** To a solution of

(14) Masuda, H.; Mihara, S. *Agric. Biol. Chem.* **1989**, *53*, 3367–3368.

2-naphthalenemethanol (1.90 g, 12.0 mmol) in 1,4-dioxane (36 mL) was added 2-chloropyridine (0.75 mL, 8.0 mmol) and potassium *tert*-butoxide (1.35 g, 12.0 mmol). The reaction vessel was equipped with an air condenser and warmed to 98 °C. After 18 h, the reaction mixture was cooled to room temperature and ethyl acetate (10 mL) and H<sub>2</sub>O (10 mL) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were then washed successively with 1:1 brine/H<sub>2</sub>O (10 mL) and H<sub>2</sub>O (10 mL), dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. Purification by column chromatography (95:5 hexane/ethyl acetate) afforded 1.85 g (98%) of **2n** as a white solid. mp: 64–66 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.21–8.25 (m, 1H), 7.94 (app s, 1H), 7.84–7.89 (m, 3H), 7.61 (dt, *J* = 12.0, 4.0 Hz, 2H), 7.46–7.52 (m, 2H), 6.89–6.94 (m, 1H), 6.87 (app d, *J* = 8.0 Hz, 1H), 5.57 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.9, 147.1, 138.9, 135.1, 133.6, 133.3, 128.4, 128.2, 127.9, 127.0, 126.4, 126.2, 126.1, 117.2, 111.6, 67.9; IR (neat) 3053, 2942, 1595, 1568, 1472, 1431, 1309, 1285, 1252, 1140 cm<sup>-1</sup>; HRMS (ESI) *m/z* 236.1078 [236.1075 calcd for C<sub>16</sub>H<sub>14</sub>NO (M + H)<sup>+</sup>].

**General Procedure for the LiI-promoted Alkyl Migration.** (*N*)-(4-Methylbenzyloxy)-2-pyridone (**3b**). To 2-(4-methylbenzyloxy)pyridine (**2b**, 211 mg, 1.06 mmol) in a 1-dram vial was added LiI (71 mg, 0.53 mmol). The sealed vial containing the mixture was placed in a 100 °C bath for 8 h. The mixture was diluted with ethyl acetate (2 mL) and the resulting solution was loaded onto

silica for purification by column chromatography (ethyl acetate) to afford 205 mg (97%) of **3b** as a yellow solid. mp: 72–74 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.29 (ddd, *J* = 10.0, 6.7, 2.1 Hz, 1H), 7.24 (ddd, *J* = 6.8, 2.0, 0.7 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.60 (ddd, *J* = 9.1, 1.3, 0.7 Hz, 1H), 6.12 (td, *J* = 6.7, 1.4 Hz, 1H), 5.10 (s, 2H), 2.32 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 163.1, 139.5, 138.2, 137.4, 133.4, 130.0, 128.7, 121.5, 106.6, 51.8, 21.6; IR (neat) 3433, 2923, 2360, 2243, 1658, 1589, 1535, 1515, 1347, 1151, 1023 cm<sup>-1</sup>; HRMS (ESI) *m/z* 222.0890 [222.0895 calcd for C<sub>13</sub>H<sub>13</sub>NONa (M + Na)<sup>+</sup>].

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**Supporting Information Available:** Representative experimental procedures and characterization data for compounds **2a–q**, **3a–o**, **4–10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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