JOC The Journal of Organic Chemistry

Article

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Preparation of *N*-Alkyl 2-Pyridones via a Lithium Iodide Promoted *O*- to *N*-Alkyl Migration: Scope and Mechanism

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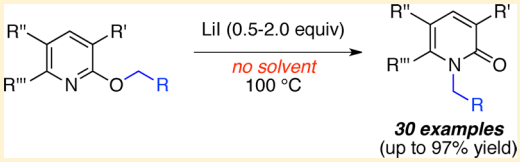
Supporting Information

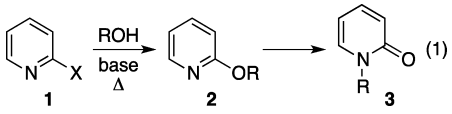
ABSTRACT: An efficient and inexpensive LiI-promoted *O*- to *N*-alkyl migration of 2-benzyloxy-, 2-allyloxy-, and 2-propargyloxypyridines and heterocycles is reported. The reaction produces the corresponding *N*-alkyl 2-pyridones and analogues under green, solvent-free conditions in good to excellent yields (30 examples, 20−97% yield). This method has been shown to be intermolecular and requires heat and lithium cation to occur.



INTRODUCTION

Enolizable heterocycles, such as 2-pyridone, have provoked significant interest in the chemical and biological communities as a result of their ability to serve as models for hydrogen bonding, tautomerization, and proton shuttling in both chemical and biological processes.[1−5] Furthermore, the presence of *N*-alkylated 2-pyridones **3** in both natural products[6−9] and pharmacologically active structures renders them important synthetic targets.[10−12] As such, the development of a simple method for selective nitrogen alkylation of 2-pyridone motifs continues to be desirable. Although direct intermolecular alkylation of either 2-hydroxypyridine or 2-pyridone has been explored, *O*-alkylation is often a competing process due to the aromatic character of the 2-oxypyridine anion.[13] Previous efforts by others in this area have utilized salts[14,15] or phase transfer catalysts[16] to help control the regiochemistry of the addition; however, these methods are largely limited to activated electrophiles and often require specific substituents on the pyridone for selectivity to be observed.

In an attempt to circumvent these problems, *O*-alkylated pyridines **2** have been explored as a means for accessing *N*-alkyl pyridones **3** (eq 1). This is a particularly attractive strategy



given that pyridines **2** can be accessed directly and in high yield from 2-halopyridines **1** and an appropriate alcohol via nucleophilic aromatic substitution. The first oxygen to nitrogen migration in a 2-alkoxy-1*N*-heterocyclic system was reported by Ikehara and Tanaka in 1974 within a nucleoside motif.[17] Since that time, *O*-alkylated 2-hydroxypyridines have been utilized in the presence of various catalysts as activated nucleophiles for nitrogen alkylation.[18,19] Even with activation, however, a sufficiently nucleophilic heterocycle is still required, as initial pyridinium salt formation occurs prior to C−O bond cleavage. In the past few years, several metal-catalyzed benzyl migrations leading to the formation of *N*-benzyl pyridones have also appeared, including both LiI- and Ru-catalyzed methods.[20,21] The former was developed in our laboratory and serves as the basis for the following account. Additionally, several Pd- and Pt-catalyzed procedures have also appeared for the preparation of *N*-allyl 2-pyridones from 2-allyloxypyridines (eq 1, R = allyl).[22−26]

Herein we report the use of LiI as an inexpensive catalyst for the efficient *O*- to *N*-alkyl migration of 2-benzyloxy-, 2-allyloxy-, and 2-propargyloxypyridines and heterocycles to provide *N*-alkyl 2-pyridones. Due to the absence of solvent in these transformations, this method represents a green alternative for the synthesis of functionalized heterocyclic motifs. These studies include both the scope of the LiI-catalyzed migration as well as efforts to elucidate the mechanism of the benzyl migration. The method reported achieves a formal [1,3]-alkyl migration for a wide range of activated substituents in good to excellent yields and with complete consumption of the starting *O*-alkylated pyridines.

RESULTS AND DISCUSSION

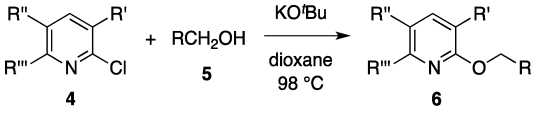
The synthesis of the required 2-alkyloxypyridines **6** was generally accomplished, as previously described, by treating 2-chloropyridine (**4**) (or a substituted analogue) with the

Received: July 26, 2012
Published: August 28, 2012

   dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220−8230

requisite alcohol in the presence of potassium *tert*-butoxide (Table 1).[20] In this way, a variety of substituted benzyl, allyl, and propargyl alcohols were readily incorporated into the pyridine scaffolds.

Table 1. Synthesis of 2-Alkoxypyridines



4 6

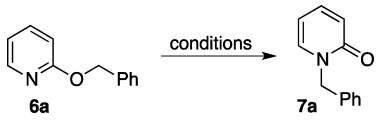
entry	R	R′	R″	R‴	product	yield (%)[a,b]
1	Ph	H	H	H	**6a**	77[c]
2	4-MeC$_6$H$_5$	H	H	H	**6b**	92[c]
3	4-MeOC$_6$H$_5$	H	H	H	**6c**	89[c]
4	4-ClC$_6$H$_5$	H	H	H	**6d**	93[c]
5	4-CO$_2$MeC$_6$H$_5$	H	H	H	**6e**	32
6	4-CF$_3$C$_6$H$_5$	H	H	H	**6f**	89
7	4-CNC$_6$H$_5$	H	H	H	**6g**	54
8	3-MeC$_6$H$_5$	H	H	H	**6h**	91[c]
9	3-MeOC$_6$H$_5$	H	H	H	**6i**	97[c]
10	3-ClC$_6$H$_5$	H	H	H	**6j**	94[c]
11	2-MeC$_6$H$_5$	H	H	H	**6k**	84[c]
12	2-MeOC$_6$H$_5$	H	H	H	**6l**	87[c]
13	2-ClC$_6$H$_5$	H	H	H	**6m**	97[c]
14	2,6-Cl$_2$C$_6$H$_4$	H	H	H	**6n**	99[c]
15	2-naphthyl	H	H	H	**6o**	98[c]
16	Ph	Me	H	H	**6p**	98[c]
17	Ph	H	Me	H	**6q**	78[c]
18	Ph	H	H	Me	**6r**	91
19	*α*-Me-Ph	H	H	H	**6s**	89[c]
20	(*E*)-CH=CH(CH$_2$)$_2$Ph	H	H	H	*E*-**6t**	77
21	(*Z*)-CH=CH(CH$_2$)$_2$Ph	H	H	H	*Z*-**6t**	85
22	C≡C(CH$_2$)$_4$CH$_3$	H	H	H	**6u**	95
23	C≡C(CH$_2$)$_2$Ph	H	H	H	**6v**	90
24	C≡CCy	H	H	H	**6w**	94
25	C≡CPh	H	H	H	**6x**	58
26	C≡C(CH$_2$)$_4$CH$_3$	Me	H	H	**6y**	91
27	C≡C(CH$_2$)$_4$CH$_3$	H	Me	H	**6z**	60
28	C≡C(CH$_2$)$_4$CH$_3$	H	H	Me	**6aa**	75
29	C≡CCH$_2$OTIPS	H	H	H	**6bb**	79[d]

[a]Conditions: 2-chloropyridine or a substituted analogue (1.0 equiv), ROH (1.5 equiv), KO^{t}Bu (1.5 equiv), 1,4-dioxane (0.22 M), 98 °C, overnight. [b]Isolated yields. [c]Reference 20. [d]Conditions: 2-fluoropyridine (1.0 equiv), ROH (1.5 equiv), KO^{t}Bu (1.5 equiv), 1,4-dioxane (0.66 M), 98 °C, overnight.

Optimization. Initial efforts to convert 2-benzyloxypyridine (**6a**) to pyridone **7a** focused on the use of various additives at elevated temperature (Table 2). Using microwave heating, TFA, BF$_3$·OEt$_2$, and LiI were each examined as possible catalysts for the transformation (entries 1–3). While all three species were found to facilitate the formation of the desired product **7a**, benzylacetamide was observed as a byproduct in the presence of either TFA or BF$_3$·OEt$_2$.[27] As this byproduct was not observed in the LiI-promoted case, LiI was targeted for further development.

Utilizing conventional heating, the efficiency of the LiI-catalyzed reaction improved with increased concentration, allowing for both the temperature and LiI loading to be decreased (Table 2, entries 4–9). Under optimum conditions, complete conversion to pyridone **7a** could be achieved in only

Table 2. Optimization of Benzyl Migration



6a 7a

entry	additive (equiv)	solvent (M)	temp (°C)	**6a**:**7a**[a,b]
1	TFA (1.0)	CH$_3$CN (0.26)	200[c]	1:5[d]
2	BF$_3$·Et$_2$O (0.1)	CH$_3$CN (0.26)	150[c]	1.8:1[d]
3	LiI (3.0)	CH$_3$CN (0.26)	200[c]	1:3
4	LiI (3.0)	CH$_3$CN (0.26)	150[e]	2.5:1
5	LiI (1.5)	CH$_3$CN (0.53)	150[e]	0:1
6	LiI (1.5)	CH$_3$CN (0.53)	100[e]	1:6
7	LiI (1.5)	none	100[e]	0:1
8	LiI (0.5)	none	100[f]	0:1
9	LiI (0.25)	none	100[e]	1:3
10	none	none	100[e]	1:0
11	LiI (0.5)	none	rt[g]	1:0

[a]Determined by either HPLC or ^{1}H NMR analysis. [b]Reference 20. [c]Microwave heating for 10 min. [d]Benzylacetamide formed as a byproduct. [e]Conventional heating for 26 h. [f]Conventional heating for 8 or 26 h [g]rt = room temperature.

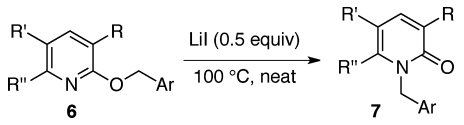
8 h with 0.5 equiv of LiI at 100 °C if the solvent was removed completely (entry 8). Finally, entries 10 and 11 reveal that the migration requires both LiI and heat to occur. Considering that 2-pyridones are known to be more thermodynamically stable than their pyridine analogues, the absence of any thermally promoted migration after 26 h at 100 °C is significant.[28,29] It should also be noted that while the removal of solvent was initially implemented to improve the efficiency of the migration, the absence of solvent also renders the reaction more environmentally benign.

Substrate Scope. Applying the optimized reaction conditions to a series of differently substituted 2-benzyloxypyridine analogues **6** allowed for the rapid preparation of a variety of substituted *N*-benzyl 2-pyridones **7** (Table 3). Monosubstitution at any position on the aryl ring was well tolerated, providing the desired products in 60–97% yield (entries 1–12). For substrates bearing electron-withdrawing groups, longer reaction times (26 h versus 8 h) generally gave higher yields (entries 4–6 and 9). Even in cases where the reactions were complete in only 8 h, the *N*-benzyl pyridone products are stable under the reaction conditions and can be isolated in similar yields after more prolonged heating.[20] Further, the reaction proceeds efficiently even in the presence of substitution at the ortho position, as shown by the reaction of 2-(2,6-dichlorobenzyloxy)pyridine (**6n**), which undergoes alkyl migration in 72% isolated yield after 26 h (entry 13). In this case, the decrease in yield is likely attributable to the electron-withdrawing ability of the two chlorine substituents rather than a steric limitation and can be overcome by simply utilizing a full equivalent of LiI (entry 14). Electron-rich 2-naphthyloxypyridine (**6o**) underwent efficient conversion under the standard reaction conditions to give *N*-2-naphyl-2-pyridone (**7o**) in 95% yield after 8 h (entry 15).

In contrast, when the heterocycle or benzylic position was substituted, the reaction was less robust. Whereas 5-methyl-substituted pyridine **6q** afforded a 93% yield of product **7q** under the standard migration conditions, the 3-methyl- and 6-methyl-substituted cases gave reduced yields (entries 16–18). Interestingly, 6-methyl pyridine **6r**, which has been found by others to be unreactive in this type of transformation,[21]

dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220–8230

Table 3. Preparation of Substituted *N*-Benzyl 2-Pyridones



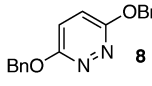
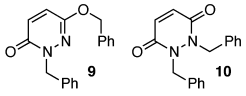
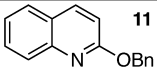
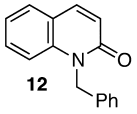
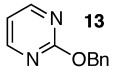
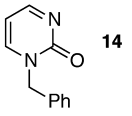
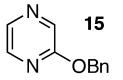
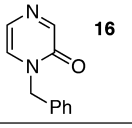
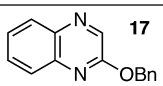
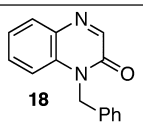
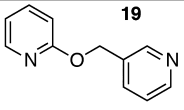
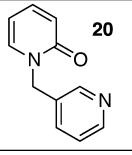
entry	substrate	Ar	R	R′	R″	product	yield[a,b]
1	**6a**	Ph	H	H	H	**7a**	91[c]
2	**6b**	4-MeC_6H_5	H	H	H	**7b**	97[c]
3	**6c**	4-MeOC_6H_5	H	H	H	**7c**	84[c]
4	**6d**	4-ClC_6H_5	H	H	H	**7d**	90[c,d]
5	**6f**	4-$CF_3C_6H_5$	H	H	H	**7f**	84[d]
6	**6g**	4-CNC_6H_5	H	H	H	**7g**	60[d]
7	**6h**	3-MeC_6H_5	H	H	H	**7h**	96[c]
8	**6i**	3-MeOC_6H_5	H	H	H	**7i**	94[c]
9	**6j**	3-ClC_6H_5	H	H	H	**7j**	93[c,d]
10	**6k**	2-MeC_6H_5	H	H	H	**7k**	91[c]
11	**6l**	2-MeOC_6H_5	H	H	H	**7l**	88[c]
12	**6m**	2-ClC_6H_5	H	H	H	**7m**	79[c]
13	**6n**	2,6-$Cl_2C_6H_4$	H	H	H	**7n**	72[c,d]
14	**6n**	2,6-$Cl_2C_6H_4$	H	H	H	**7n**	85[c,e]
15	**6o**	2-naphthyl	H	H	H	**7o**	95[c]
16	**6p**	Ph	Me	H	H	**7p**	57[c,d,e]
17	**6q**	Ph	H	Me	H	**7q**	93[c]
18	**6r**	Ph	H	H	Me	**7r**	59[d]
19	**6s**	α-Me-Ph	H	H	H	**7s**	34[c,d]

[a]Conditions: substrate (1.0 equiv), LiI (0.5 equiv), 100 °C, 8 h. [b]Isolated yields. Mean values from duplicate experiments (±3%). [c]Reference 20. [d]Reaction duration = 26 h. [e]1.0 equiv of LiI used.

provided 59% yield of the desired pyridone **7r** after 26 h (entry 18). However, 3-methyl pyridine **6p** required both 26 h and a full equivalent of LiI to give comparable results (entry 16). In a similar manner, 2-(α-methylbenzyloxy)pyridine (**6s**), which bears substitution at the benzylic position, undergoes migration more slowly than the unsubstituted case, affording only 34% yield after 26 h (entry 19). While this yield is low, the occurrence of the transformation is significant, given that substrates with benzylic substituents have failed to react under other established protocols.[21] The reduced yield in each of these cases is likely the result of a negative steric interaction imposed by the appended methyl group.

Application of these conditions to other *N*-heterocycles, including heterocycles with additional nitrogen atoms, resulted in less successful migration reactions (Table 4). While dibenzyl pyridazine derivative **8** was found to undergo mono- and dimigration when subjected to 0.5 equiv LiI for 26 h in 63% and 6% yields, respectively, heterocycles **11**, **13**, **15**, and **17** showed little or no reactivity under these conditions. By increasing the amount of LiI and the temperature, quinolone **12** and pyrimidone **14** could be isolated in 71% and 61% yields, respectively (entries 2 and 3). Unfortunately, the reaction of pyrazine **15** and quinoxaline **17** produced far greater amounts of unidentified byproducts, leading to lower overall yields of the migration products **16** and **18** (entries 4 and 5). 3-Pyridyl-substituted pyridine **19** was the least productive of these analogues, providing an array of unidentified byproducts and none of the desired pyridone **20** (entry 6). In these cases, the

Table 4. Evaluation of Heterocyclic Analogues

entry	substrate	conditions[a]	product	yield (%)[b]
1		A		63 (**9**); 6 (**10**)
2		B		71[c]
3		C		61[c]
4		D		39[c]
5		B		20[c]
6		A		NP[c,d]

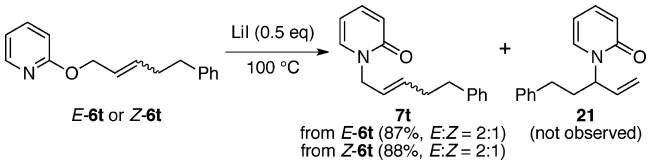
[a]Conditions: (A) substrate (1.0 equiv), LiI (0.5 equiv), 100 °C, 26 h. (B) substrate (1.0 equiv), LiI (1.0 equiv), 110 °C, 26 h. (C) substrate (1.0 equiv), LiI (1.0 equiv), 100 °C, 26 h. (D) substrate (1.0 equiv), LiI (2.0 equiv), 110 °C, 26 h. [b]Isolated yields. Mean values from duplicate experiments (±3%). [c]Reference 20. [d]NP = no product identified.

dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220−8230

inclusion of an additional basic nitrogen away from the alkoxy substituent seems to hinder the desired alkyl migration.

In an attempt to extend our methodology to other activated groups, 2-allyloxypyridines **6t** were also evaluated and shown to migrate in good yields (Scheme 1). When geometrically pure *E*-

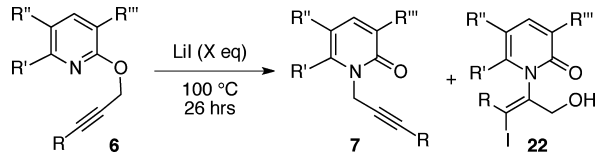
Scheme 1. LiI-Catalyzed Allyloxypyridine Migration



allyloxypyridine *E*-**6t** was subjected to the migration conditions, a 2:1 mixture of *E*- and *Z*-*N*-alkylated 2-pyridone **7t** was observed in 87% yield. A similar result was observed when the *Z*-isomer was utilized (2:1 ratio *E*-**7t**:*Z*-**7t**, 88% yield). These results suggest the formation of a common carbocation intermediate in the allyl migration. Further, although a [3,3]-sigmatropic rearrangement can also be envisaged at these temperatures, no spectral evidence for terminal alkene **21** was observed after heating alkene **6t** in either the presence or absence of lithium iodide. The preference for formation of linear product **7t** over branched product **21** is expected to be largely thermodynamically driven.

Propargyloxypyridines **6u**–**6bb** were also subjected to the alkyl migration conditions (LiI (0.5–2.0 equiv), 100 °C, neat, 26 h, Table 5). In all cases, 2-propargyloxypyridines **6** were found to undergo migration more slowly than the corresponding benzyl-substituted analogues (26 versus 8 h). In addition,

Table 5. Formation of *N*-Propargyl 2-Pyridones



entry	substrate	R	R′	R″	R‴	LiI (equiv)	yield 7 (%)[a]
1	**6u**	pentyl	H	H	H	0.5	81
2	**6v**	CH_2CH_2Ph	H	H	H	0.5	55
3	**6v**	CH_2CH_2Ph	H	H	H	0.8	85
4	**6v**	CH_2CH_2Ph	H	H	H	1.0	84
5	**6w**	Cy	H	H	H	0.5	36
6	**6w**	Cy	H	H	H	0.8	56
7	**6w**	Cy	H	H	H	1.2	77
8	**6x**	Ph	H	H	H	0.5	19
9	**6x**	Ph	H	H	H	1.4	53
10	**6x**	Ph	H	H	H	2.0	66
11	**6y**	pentyl	Me	H	H	0.5	NP[b]
12	**6z**	pentyl	H	Me	H	0.5	57
13	**6z**	pentyl	H	Me	H	1.0	64
14	**6z**	pentyl	H	Me	H	1.5	56
15	**6aa**	pentyl	H	H	Me	0.5	15
16	**6bb**	CH_2OTIPS	H	H	H	0.5	–[c]
17	**6bb**	CH_2OTIPS	H	H	H	1.0	–[d]
18	**6bb**	CH_2OTIPS	H	H	H	1.5	–[e]

[a]Isolated yields. Mean value of duplicate runs (±3%). [b]NP = no product identified. [c]13% yield **22bb**; 70% **6bb** recovered. [d]16% yield **22bb**; 55% **6bb** recovered. [e]16% yield **22bb**; <10% **6bb** recovered.

many of the substrates required superstoichiometric amounts of LiI to proceed efficiently.

In general, utilizing 1.0 equiv LiI at 100 °C for 26 h represents good initial conditions for the propargyl migration; however, the ideal amount of LiI can be optimized independently for each substrate (Table 5). Using this technique, conditions were identified in which a variety of 2-propargyloxypyridines **6** underwent migration to give the desired pyridone products **7** in good to excellent yields (66–85%, entries 1–10). The reaction tolerates a range of substitution on the alkyne terminus, including some with significant steric bulk, including cyclohexyl substrate **6w**. In these sterically congested systems, the yield was found to increase when more LiI was used (entries 3 and 7). The migration was also found to occur in the presence of extended conjugation, as phenyl substrate **6x** undergoes migration to give pyridone **7x** in 66% yield in the presence of 2.0 equiv of LiI (entry 10).

As with the benzyl migration, added substitution on the pyridine ring was met with mixed results. While methyl substitution at C5 on the pyridine ring was found to have a minimal effect on the migration (64% yield, entry 13), methylation at either C3 or C6 was significantly more detrimental with no more than 15% of the desired pyridone isolated (entries 11 and 15). In these cases, it is assumed that the additional substitution interferes with coordination of lithium to the heteroatoms and thus impedes the migration.

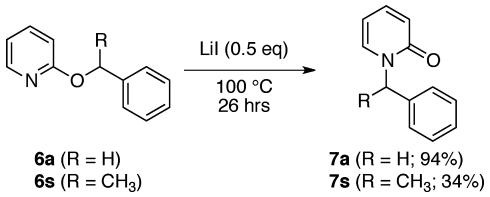
Throughout these studies, it was observed that a small amount of β-iodo *N*-alkenyl pyridone **22** was generally formed in addition to the desired *N*-propargyl pyridone **7**. This byproduct was first observed in 2-octynyl substrate **6u**, and a full report detailing the synthesis of this class of compounds has appeared elsewhere.[30] Interestingly, in the case of silyl ether **6bb**, *N*-alkenyl pyridone **22bb** was observed as the only product of the reaction in low isolated yields (entries 16–18). In this case, increasing the amount of LiI did little to improve the reaction yield but did decrease the amount of starting pyridine **6bb** that was recovered (0.5 equiv LiI: 13% **22bb**, 70% **6bb** recovered; 1.0 equiv LiI: 16% **22bb**, 55% **6bb** recovered; 1.5 equiv LiI: 16% **22bb**, <10% **6bb** recovered).

Mechanistic Studies. Unlike the allyl migration, benzyl migration does not appear to proceed through a carbocation intermediate. This conclusion stems from the initial optimization studies in which no benzylacetamide byproduct was observed in the presence of LiI, as compared to either TFA or $BF_3{\cdot}OEt_2$, (see Table 2). The formation of benzylacetamide is expected to occur upon Ritter reaction between benzyl cation and the acetonitrile solvent. Further, 2-(α-methylbenzyloxy)-pyridine (**6s**) would be predicted to undergo a more facile migration if a stable secondary benzylic carbocation was being formed; however, this substrate proceeds with much lower efficiency than the corresponding unsubstituted case (Scheme 2). Thus, additional benzylic substitution appears to inhibit product formation rather than accelerate it.

Given this departure from our initial expectation, a Hammett plot was constructed for the migration of *para*-substituted 2-benzyloxypyridines **6**. In this way, we hoped to gain an understanding of the type of intermediates that were involved in the reaction. Utilizing seven different *para*-substituted benzyloxypyridines **6**, the required kinetic data was obtained by ^{1}H NMR analysis of reaction aliquots. Reactions were performed at 90 °C (standard conditions = 100 °C) in order to decrease the reaction rate and allow for reproducible data to be

dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220–8230

Scheme 2. Impact of Benzylic Substitution on Migration Efficiency



collected. Using this data, a Hammett plot was generated displaying $\rho = -2.60$ ($R^2 = 0.89$, Figure 1). This large negative

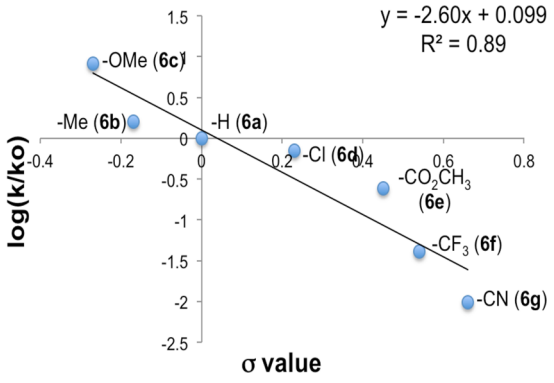


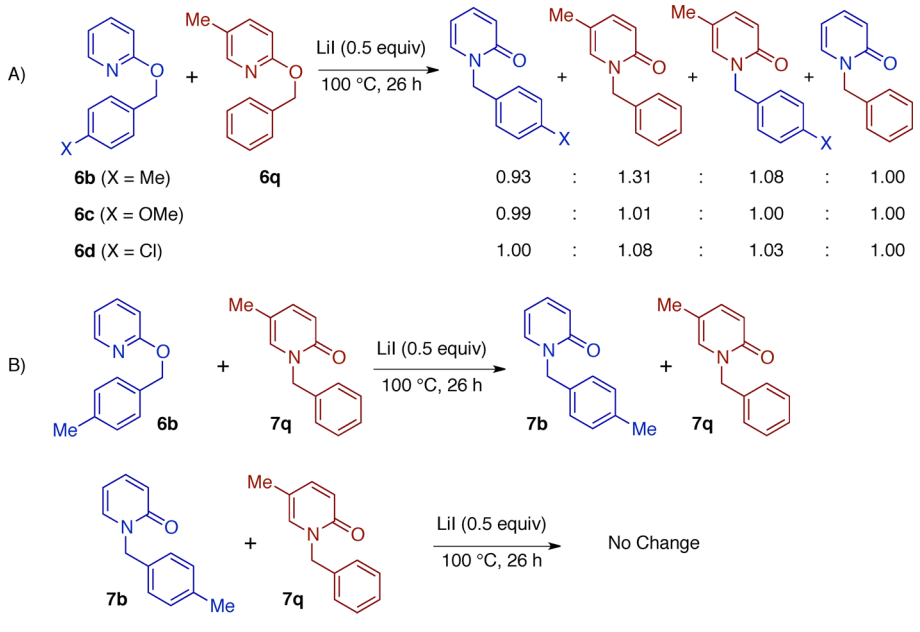
Figure 1. Hammett plot for the LiI-catalyzed migration of *para*-substituted benzyloxypyridines **6**.

ρ value strongly suggests that the reaction is proceeding through an electrophilic intermediate and provides strong evidence against mechanisms in which a negatively charged, radical (neutral), or intramolecular (neutral) intermediate would be required before or at the rate-determining step. The large negative ρ value could be consistent with a number of different electrophilic pathways, including nucleophilc benzyl displacement or formation of a benzylic carbocation in the rate-determining step.

In order to provide further evidence against an intramolecular process, crossover experiments between methylated pyridine **6q** and *para*-substituted methyl-, methoxy-, and chloro-substituted benzyloxypyridines **6b**–**6d** were conducted (Scheme 3A). In each case, all four possible crossover products were observed, eliminating the possibility that the migration is intramolecular. Perhaps most interesting, however, was the close to equimolar amounts of all four crossover products observed in each of these transformations as determined by ^{1}H NMR. This is particularly intriguing since the methoxybenzyl substrate **6c** and chlorobenzyl substrate **6d** migrate at significantly different rates, as demonstrated in the Hammett plot in Figure 1. Further control experiments in which either equimolar amounts of benzyloxypyridine **6a** and substituted pyridone **7q** or alternatively pyridones **7b** and **7q** were subjected to the reaction conditions provided no products resulting from crossover (Scheme 3B). These results suggest that exchange must occur during the initial alkyl migration and that this migration is not reversible under the reaction conditions. Further, these observations stand in contrast to the intramolecular Ru-catalyzed benzyl migration reported by Dong and co-workers, in which no crossover is observed.[21]

Two distinct non-carbocation mechanisms appear to be consistent with the observed data: (A) formation of a benzyl iodide intermediate upon cleavage of the C–O bond by nucleophilic iodide and then capture by an anionic pyridone (Scheme 4A) or (B) nucleophilic cleavage of the C–O bond by the nitrogen of another molecule of benzyloxypyridine (BOP) **6**, either directly or through a more highly organized dimeric complex (Scheme 4B). In each of these cases, it is assumed that initial precoordination of lithium is required for migration to take place. Complexes **23**, **24**, and **25**, as proposed in mechanistic possibility B, would in fact require lithium to coordinate to two, three, or four heteroatoms rather than just a single oxygen atom.[31] The formation of more complex dimers **24** and **25** may be facilitated by the presence of one or more edge-to-face aromatic–aromatic interactions (see green interactions in Scheme 4B).[32] In the case of mechanism B, iodide

Scheme 3. Crossover Experiments



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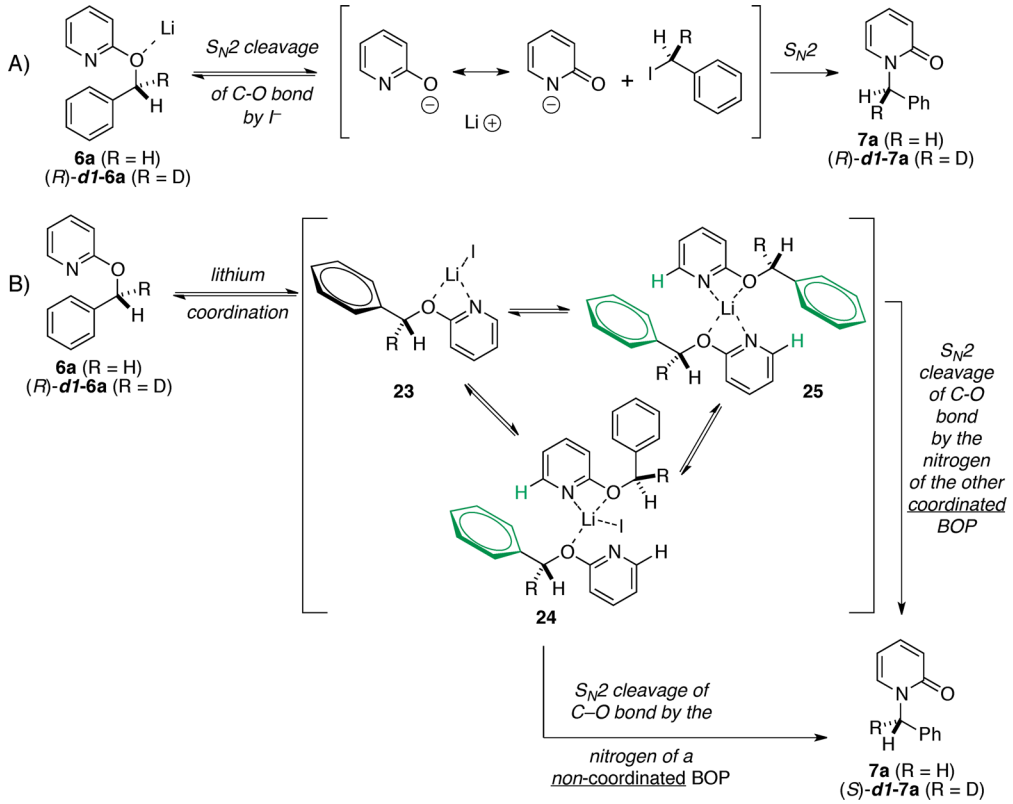
Scheme 4. Possible Non-Carbocation Mechanisms for Benzyl Migration[a]

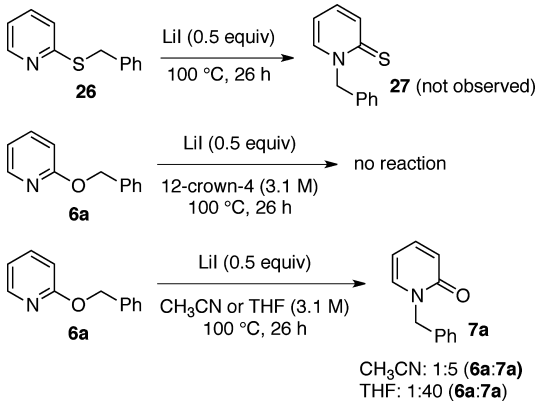


[a]Potential edge-to-face aromatic−aromatic interactions are indicated in green.

may or may not serve as a ligand for lithium during the migration.

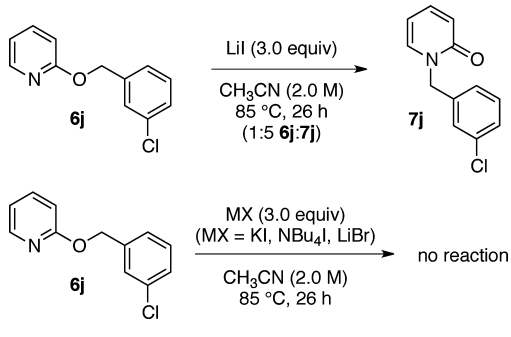
To secure the importance of lithium in the migration, two parallel studies were conducted. First, 2-benzylthiopyridine **26** was subjected to the migration conditions (0.5 equiv LiI, 100 °C, Scheme 5). In this case, the thiopyridone **27** was not observed, although sulfur analogue **26** was recovered unchanged. Given the lower affinity of sulfur for lithium, this strongly suggests that lithium coordination to the oxygen is required for migration to occur. Further evidence in support of this result was garnered when benzyloxypyridine **6a** was treated with LiI in the presence of 2 equiv of 12-crown-4 (reaction concentration = 3.1 M). In this case, only starting material was recovered. In order to ensure that this observation was not a solvent effect, the reaction was performed with CH_3CN or THF as solvent at the same concentration. In these cases, significant migration was observed by ^1H NMR (1:5 and 1:40 **6a**:**7a**, respectively). The lack of reactivity of the sulfur analogue **26** and the recovery of pyridine **6a** unchanged in the presence of 12-crown-4 both, independently, confirm the importance of lithium cation in the migration.

Scheme 5. Importance of Lithium Coordination to the Alkyl Migration



The role of iodide in the reaction, however, remains less clear. While the migration of pyridine **6j** proceeds smoothly in the presence of LiI, other iodide salts (KI and NBu_4I) gave none of the expected pyridone **7j** (Scheme 6). In these reactions, CH_3CN was added to ensure the solubility of each salt. Interestingly, migrations conducted under these conditions in the presence of LiBr also yielded only recovered starting material, suggesting that the unique dissociative properties of

Scheme 6. Evaluation of Various Metal Salts

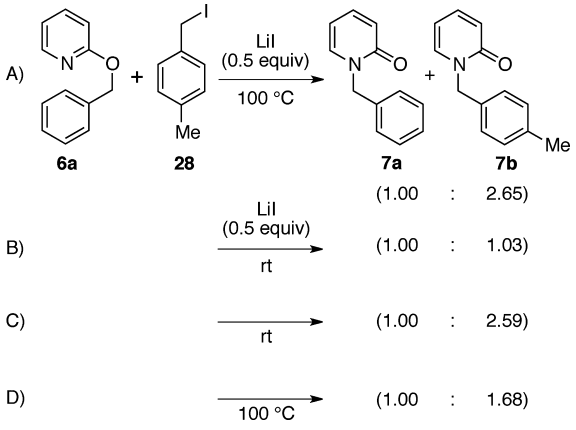


dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220−8230

LiI may be as important to the reaction as the iodide counterion.

Further efforts to discern the importance of iodide in the reaction focused on the addition of methylated benzyl iodide **28** to the standard reaction with benzyloxypyridine **6a** (Scheme 7A).[33] When pyridine **6a** and tagged benzyl iodide **28** were

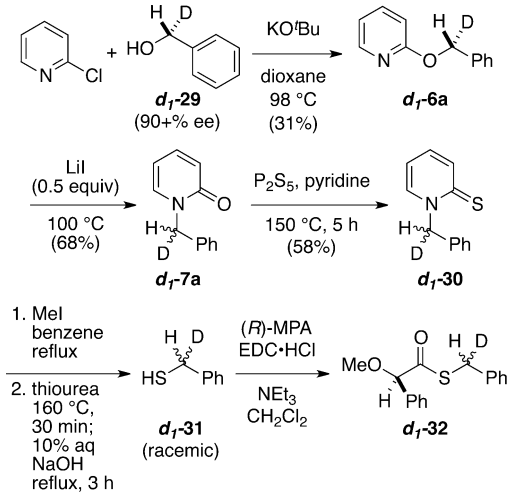
Scheme 7. Incorporation of 4-Methyl Benzyl Iodide 28



mixed in a 1:1 ratio in the presence of 0.5 equiv of LiI, ^{1}H NMR analysis of the crude reaction mixture showed that both methylated pyridone **7b** and a smaller amount of unsubstituted pyridone **7a** had been formed. This reaction was then repeated in the presence of benzyl iodide **28** at ambient temperature with and without LiI and at 100 °C with no LiI (Scheme 7B–D). Under each set of conditions, both methylated product **7b** as well as unsubstituted pyridone **7a** were observed. That pyridone products are formed in the absence of both LiI and heat in the presence of an external benzyl electrophile, suggests that the rate determining step in the migration is likely C–O bond cleavage, as no migration is observed under these conditions in the absence of a benzyl iodide source (see Table 2, entry 11 for comparison). Further, the reaction with iodide **28** shows that benzyl iodides are competent intermediates to initiate the reaction cascade, although it does not prove that such an intermediate is actually generated. The formation of unsubstituted pyridone **7a** in the reaction with external iodide **28**, however, implies that once initial alkylation of the pyridine nitrogen occurs, another molecule of benzyloxypyridine **6a** is competent to cleave the C–O bond to provide the unsubstituted product **7a**. This type of scenario would be necessary if the migration were occurring through mechanism B. As such, the presence of both methylated product **7b** and unsubstituted pyridone **7a** imply that either mechanism A or B could be operative.

In an effort to differentiate between these possibilities, an enantioenriched monodeuterated 2-benzyloxypyridine ***d*$_1$-6a** was subjected to the reaction conditions (Scheme 8). Since mechanism A is expected to proceed through two sequential S_N2 displacements and mechanism B would only require a single S_N2 displacement, subjecting such a labeled substrate to the migration conditions was expected to allow these mechanistic possibilities to be distinguished (see Scheme 4). Using Noyori's ruthenium transfer hydrogenation protocol,[34,35] monodeuterated benzyl alcohol ***d*$_1$-29** was prepared in 90+% ee, as determined by MTPA ester analysis.[36] Incorporation of alcohol ***d*$_1$-29** into chiral pyridine ***d*$_1$-6a** and treatment under the standard migration conditions provided deuterated *N*-

Scheme 8. Determination of the Stereochemical Outcome of Benzyl Migration



benzyl pyridone ***d*$_1$-7a** in 68% isolated yield. Interestingly, pyridone ***d*$_1$-7a** is formed as a 1:1 mixture of two rotational isomers around the C–N bond, as determined by ^{13}C NMR analysis. This suggests that pyridone ***d*$_1$-7a** is formed as a racemate, as the nonlabeled pyridone **7a** does not exhibit this characteristic. Isotopically labeled pyridone ***d*$_1$-7a** was then treated with P_2S_5 to provide thiopyridone ***d*$_1$-30**.[37] Subsequent exposure of compound ***d*$_1$-30** to MeI provided the thiomethyl pyridinium salt,[37] which was then treated with thiourea to facilitate cleavage of the benzyl group via an expected S_N2 process.[38] Hydrolysis in aqueous base then provided the deuterated benzyl mercaptan ***d*$_1$-31**. Preparation and stereochemical analysis of the (*R*)-MPA thioester ***d*$_1$-32** by ^{1}H NMR revealed that the isolated benzyl mercaptan ***d*$_1$-31** was racemic,[39] as demonstrated by the presence of two singlets of equal intensity at 3.94 and 4.02 ppm.[40] While initially unexpected, this result suggests that either the two nucleophilic displacement mechanisms are operating in tandem to accomplish the formal [1,3]-benzyl migration or that at some point in the migration process a carbocation is in fact being formed. Such a carbocation could result from the ionization of a benzyl iodide intermediate under the reaction conditions (100 °C) or through the formation of a benzyl cation that has gone undetected in our investigations due to rapid recombination. A reversible migration could also produce this result, however, since no crossover is observed when differently substituted pyridones are subjected to the migration conditions, this seems unlikely (see Scheme 3B).

In summary, the LiI-catalyzed benzyl migration has been shown to proceed via an intermolecular process that relies on the activation of the benzyloxypyridine by lithium. While two distinct nucleophilic displacement mechanisms are possible and would be expected to give two stereochemically distinct products, isotopically labeled pyridine ***d*$_1$-6a** was found to undergo migration to afford pyridone ***d*$_1$-7a** as a racemate, suggesting that these two processes are either operating in tandem or that the reaction proceeds through an otherwise undetected carbocation.

■ CONCLUSION

We have reported an inexpensive and efficient LiI-catalyzed alkyl migration of 2-benzyloxy-, 2-allyloxy-, and 2-propargyloxy-

dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220–8230

pyridines and heterocyclic analogues that proceeds under green conditions to afford the corresponding *N*-alkyl 2-pyridones in good to excellent yields. This method has been shown to require heat and lithium cation to occur and proceeds through either a combination of nucleophilic displacement mechanisms or a short-lived carbocation. Despite some limitations, this transformation provides an excellent means for the preparation of *N*-alkyl pyridones and heterocyclic analogues and should find wide synthetic application.

EXPERIMENTAL SECTION

All reagents were purchased from commercial venders and used as received. ^{1}H and ^{13}C NMR spectra were obtained on either a 400 MHz or 500 MHz NMR spectrometer. Chemical shifts are reported in ppm relative to $CDCl_3$. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); dt (doublet of triplets); app (apparent).

General Experimental Procedure for the Synthesis of 2-Alkoxypyridines. 2-Benzyloxy-6-methylpyridine (6r). To a solution of benzyl alcohol (2.07 mL, 20.0 mmol) in 1,4-dioxane (45 mL) were added 2-chloro-6-methylpyridine (1.09 mL, 10.0 mmol) and potassium *tert*-butoxide (1.68 g, 15.0 mmol). The reaction vessel was equipped with an air condenser and warmed to 98 °C. After 19 h, the reaction mixture was cooled to room temperature, and ethyl acetate (10 mL) and H_2O (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_2O (10 mL) and H_2O (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (39:1 hexane/ethyl acetate) afforded 1.80 g (91% yield) of **6r** as a white solid: mp 39−40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.50 (m, 3H), 7.37 (tt, J = 1.2, 7.1 Hz, 2H), 7.28−7.34 (m, 1H), 6.72 (d, J = 7.2 Hz, 1H), 6.59 (d, J = 8.2 Hz, 1H), 5.37 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 156.2, 138.8, 137.6, 128.4, 128.1, 127.7, 115.9, 107.6, 67.4, 24.2; IR (neat) 3065, 3032, 2952, 1599, 1575, 1451, 1304, 1232 cm^{-1}; HRMS (ESI-TOF) m/z 222.0891 [222.0895 calcd for $C_{13}H_{13}NONa$ (M + Na)$^+$].

Methyl 4-(2-Pyridinyloxymethyl)benzoate (6e). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (2.02 g, 18.0 mmol) was added to 2-chloropyridine (1.13 mL, 12.0 mmol) and methyl 4-(hydroxymethyl)-benzoate (2.99 g, 18.0 mmol) in 1,4-dioxane (54.5 mL). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 9:1 hexanes/ethyl acetate) to afford 923 mg (32% yield) of **6e** as a white solid: mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 4.7 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.57 (t, J = 7.1 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 6.87 (t, J = 6.4 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 5.42 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 163.2, 146.8, 142.7, 138.7, 129.7, 129.4, 127.3, 117.1, 111.2, 66.6, 52.1; IR (neat) 3032, 2952, 1722, 1598, 1474, 1434, 1278, 1109 cm^{-1}; HRMS (ESI-TOF) m/z 244.0973 [244.0974 calcd for $C_{14}H_{14}NO_3$ (M + H)$^+$].

2-(4-Trifluoromethylbenzyloxy)pyridine (6f). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (1.01 g, 9.00 mmol) was added to 2-chloropyridine (0.56 mL, 6.00 mmol) and 4-trifluoromethylbenzyl alcohol (1.23 mL, 9.00 mmol) in 1,4-dioxane (27.3 mL). After 16 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 1.35 g (89% yield) of **6f** as a white solid: mp 38−39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (app dd, J = 2.0, 5.1 Hz, 1H), 7.55−7.65 (m, 5H), 6.90 (app dd, J = 5.1, 7.1 Hz, 1H), 6.83 (qd, J = 0.6, 8.4 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 146.8, 141.6, 138.8, 129.1 (q, J = 32.4 Hz), 127.8, 125.6 (q, J = 3.7 Hz), 122.8, 117.2, 111.2, 66.5; IR (neat) 3016, 2939, 1594, 1569, 1473, 1432, 1325, 1270, 1121 cm^{-1}; HRMS (ESI-TOF) m/z 254.0789 [254.0793 calcd for $C_{13}H_{11}F_3NO$ (M + H)$^+$].

2-(4-Cyanobenzyloxy)pyridine (6g). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (505 mg, 4.50 mmol) was added to 2-chloropyridine (0.28 mL, 3.00 mmol) and 4-(hydroxymethyl)benzonitrile (601 mg, 4.50 mmol) in 1,4-dioxane (13.6 mL). After 20 h, the reaction was worked up and purified by column chromatography (SiO_2, 4:1 hexanes/ethyl acetate) to afford 342 mg (54% yield) of **6g** as a white solid: mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (app d, J = 3.0 Hz, 1H), 7.55−7.65 (m, 3H), 7.52 (d, J = 8.0 Hz, 2H), 6.88 (app t, J = 7.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 5.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 146.8, 143.0, 138.9, 132.2, 127.9, 118.8, 117.4, 111.3, 111.2, 66.2; IR (neat) 3053, 2932, 2228, 1592, 1571, 1474, 1432, 1285 cm^{-1}; HRMS (ESI-TOF) m/z 211.0870 [211.0871 calcd for $C_{13}H_{11}N_2O$ (M + H)$^+$].

(*E*)-2-(5-Phenyl-2-pentenyloxy)pyridine (*E*-6t). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (1.97 g, 17.6 mmol) was added to 2-chloropyridine (1.10 mL, 11.7 mmol) and (*E*)-5-phenyl-2-penten-1-ol[41] (2.85 g, 17.6 mmol) in 1,4-dioxane (54 mL). After 20 h, the reaction was worked up and purified by column chromatography (SiO_2, 39:1 hexanes/ethyl acetate) to afford 2.16 g (77% yield) of *E*-**6t** as a viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (ddd, J = 1.4, 2.2, 6.5 Hz, 1H), 7.56 (ddt, J = 0.5, 2.0, 6.0 Hz, 1H), 7.25−7.30 (m, 2H), 7.15−7.21 (m, 3H), 6.86 (ddd, J = 1.0, 5.0, 6.9 Hz, 1H), 6.75 (td, J = 0.8, 8.4 Hz, 1H), 5.85−5.94 (m, 1H), 5.75−5.83 (m, 1H), 4.78 (d, J = 6.1 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 2.40 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 147.1, 142.0, 138.7, 134.6, 128.7, 128.5, 126.1, 125.9, 116.9, 111.4, 66.6, 35.7, 34.4; IR (neat) 3026, 2932, 1595, 1472, 1432, 1285 cm^{-1}; HRMS (ESI-TOF) m/z 262.1204 [262.1208 calcd for $C_{16}H_{17}NONa$ (M + Na)$^+$].

(*Z*)-2-(5-Phenyl-2-pentenyloxy)pyridine (*Z*-6t). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (426 mg, 3.80 mmol) was added to 2-chloropyridine (0.24 mL, 2.50 mmol) and (*Z*)-5-phenyl-2-penten-1-ol[41,42] (566 mg, 3.80 mmol) in 1,4-dioxane (11.4 mL). After 18 h, the reaction was worked up and purified by column chromatography (SiO_2, 32:1 hexanes/ethyl acetate) to afford 506 mg (85% yield) of *Z*-**6t** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.17 (m, 1H), 7.57 (dddd, J = 0.7, 2.0, 7.1, 8.3 Hz, 1H), 7.26−7.32 (m, 2H), 7.16−7.24 (m, 3H), 6.86 (tdd, J = 0.8, 5.1, 7.0 Hz, 1H), 6.74 (ddd, J = 0.8, 1.7, 8.4 Hz, 1H), 5.67−5.80 (m, 2H), 4.85 (d, J = 6.0 Hz, 2H), 2.74 (t, J = 7.8 Hz, 2H), 2.50 (q, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.3, 147.0, 141.8, 138.7, 133.4, 128.7, 128.6, 126.1, 125.8, 116.9, 111.5, 61.9, 36.0, 29.7; IR (neat) 3024, 2929, 1594, 1569, 1473, 1432, 1285 cm^{-1}; HRMS (ESI-TOF) m/z 262.1212 [262.1208 calcd for $C_{16}H_{17}NONa$ (M + Na)$^+$].

2-(4-Triisopropylsiloxy-2-butynyl)pyridine (6bb). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (253 mg, 2.25 mmol) was added to 2-fluoropyridine (0.13 mL, 1.50 mmol) and 4-triisopropylsiloxy-2-butyn-1-ol[43] (545 mg, 2.25 mmol) in 1,4-dioxane (2.3 mL). After 16 h, the reaction was worked up and purified by column chromatography (SiO_2, 32:1 hexanes/ethyl acetate) to afford 378 mg (79% yield) of **6bb** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 3.2 Hz, 1H), 7.55 (dt, J = 2.0, 7.0 Hz, 1H), 6.86 (app t, J = 5.1 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 4.98 (t, J = 1.7 Hz, 2H), 4.40 (t, J = 1.6 Hz, 2H), 0.96−1.16 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 146.7, 138.6, 117.2, 111.2, 84.9, 80.0, 53.6, 52.0, 17.8, 11.9; IR (neat) 2943, 2866, 1596, 1573, 1488, 1434, 1285, 1271 cm^{-1}; HRMS (ESI-TOF) m/z 342.1871 [342.1865 calcd for $C_{18}H_{29}NO_2SiNa$ (M + Na)$^+$].

General Procedure for the LiI-Promoted Rearrangement of 2-Alkoxypyridines. (*N*)-(4-Trifluoromethylbenzyloxy)-2-pyridone (7f). To 2-(4-trifluoromethylbenzyloxy)pyridine (**6f**, 210 mg, 0.83 mmol) in a 1 dram vial was added LiI (56 mg, 0.42 mmol). The sealed vial containing the mixture was placed in a 100 °C bath for 26 h. Upon removal from the bath, the mixture was diluted with ethyl acetate (2 mL), and the resulting solution was loaded onto silica gel for purification by column chromatography (SiO_2, 1:3 hexane/ethyl acetate) to afford 176 mg (84%) of **7f** as a white solid: mp 82−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.29−7.35 (m, 1H), 7.22−7.26 (m, 1H), 6.60 (d, J = 9.1 Hz, 1H), 6.16 (t, J = 6.9 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (125 MHz,

dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220−8230

$CDCl_3$) δ 162.5, 140.4 (q, J = 1.3 Hz), 139.8, 137.3, 130.0 (q, J = 32.4 Hz), 128.1, 125.7 (q, J = 3.8 Hz), 123.9 (q, J = 274 Hz), 121.3, 106.6, 51.7; IR (neat) 3065, 2917, 1665, 1586, 1536, 1325, 1108 cm^{-1}; HRMS (ESI-TOF) m/z 276.0608 [276.0612 calcd for $C_{13}H_{10}F_3NONa$ $(M + Na)^+$].

(*N*)-(4-Cyanomethylbenzyloxy)-2-pyridone (7g). Following the general procedure above for the preparation of compound **7f**, 2-(4-cyanomethylbenzyloxy)pyridine (**6g**, 174 mg, 0.83 mmol) was treated with LiI (55 mg, 0.41 mmol) for 26 h. Purification by column chromatography (SiO_2,1:1 hexanes/ethyl acetate) afforded 104 mg (60%) of **7g** as a white solid: mp 136−137 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2H), 7.28−7.36 (m, 3H), 7.24 (dd, J = 0.9, 6.7 Hz, 1H), 6.56 (d, J = 9.2 Hz, 1H), 6.16 (t, J = 6.7 Hz, 1H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 141.7, 139.9, 137.2, 132.6, 128.3, 121.4, 118.5, 111.7, 106.7, 51.9; IR (neat) 3433, 3065, 2228, 1659, 1585, 1538 cm^{-1}; HRMS (ESI-TOF) m/z 233.0699 [233.0691 calcd for $C_{13}H_{10}N_2ONa$ $(M + Na)^+$].

(*N*)-Benzyloxy-6-methyl-2-pyridone (7r). Following the general procedure above for the preparation of compound **7f**, 2-benzyloxy-6-methylpyridine (**6r**, 108 mg, 0.54 mmol) was treated with LiI (36 mg, 0.27 mmol) for 26 h. Purification by column chromatography (SiO_2,1:1 hexanes/ethyl acetate) afforded 65 mg (60%) of **7r** as a white solid: mp 103−105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18−7.31 (m, 4H), 7.12 (d, J = 7.1 Hz, 2H), 6.52 (d, J = 9.0 Hz, 1H), 6.00 (d, J = 6.9 Hz, 1H), 5.33 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 146.6, 139.1, 136.4, 128.8, 127.3, 126.4, 117.8, 107.0, 47.1, 20.6; IR (neat) 3448, 3033, 2962, 1656, 1550, 1407, 1144 cm^{-1}; HRMS (ESI-TOF) m/z 222.0888 [222.0895 calcd for $C_{13}H_{13}NONa$ $(M + Na)^+$].

(*N*)-Benzyl-6-benzyloxy-1-pyridazone (9) and (*N*,*N*)-Dibenzyl-1,4-pyridazone (10). Following the general procedure above for the preparation of compound **7f**, 3,6-dibenzyloxypyridazine (**8**,[21] 104 mg, 0.39 mmol) was treated with LiI (27 mg, 0.20 mmol) for 26 h. Purification by column chromatography (SiO_2, 1:1 hexanes/ethyl acetate) afforded 66 mg (63%) of **9** and 6 mg (6%) of **10**. Compound **9**: mp 83−84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.38 (m, 10H), 6.86−6.93 (m, 2H), 5.17 (s, 2H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 152.1, 136.4, 135.9, 133.1, 128.7, 128.51, 128.48, 128.3, 128.2, 127.7, 126.5, 68.8, 54.4; IR (neat) 3448, 3033, 2947, 1668, 1590, 1438, 1279 cm^{-1}; HRMS (ESI-TOF) m/z 315.1102 [315.1110 calcd for $C_{18}H_{16}N_2O_2Na$ $(M + Na)^+$]. Compound **10**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.35 (m, 6H), 7.02 (d, J = 7.3 Hz, 4H), 6.99 (s, 2H), 5.08 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 134.9, 134.7, 129.2, 128.2, 126.1, 48.2; IR (neat) 3484, 3033, 2924, 1641, 1595, 1455, 1285, 1136 cm^{-1}; HRMS (ESI-TOF) m/z 315.1110 [315.1110 calcd for $C_{18}H_{16}N_2O_2Na$ $(M + Na)^+$].

5-Phenyl-1-(2-pyridonyl)pent-2-ene (7t). Following the general procedure above for the preparation of compound **7f**, (*E*)-2-(5-phenyl-2-pentenyloxy)pyridine (*E*-**6t**, 354 mg, 1.48 mmol) was treated with LiI (99 mg, 0.74 mmol) for 26 h. Purification by column chromatography (SiO_2, ethyl acetate) afforded 207 mg (58%) of *E*-**7t** and 101 mg (29%) of *Z*-**7t** as viscous orange oils.[44] Compound *E*-**7t**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.09−7.32 (m, 7H), 6.56 (ddd, J = 0.7, 1.3, 9.1 Hz, 1H), 6.11 (td, J = 1.4, 6.7 Hz, 1H), 5.67−5.76 (m, 1H), 5.52−5.61 (m, 1H), 4.48 (dd, J = 1.0, 6.3 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.39 (app q, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 141.6, 139.5, 137.0, 135.2, 128.7, 128.6, 126.1, 125.2, 121.1, 106.2, 50.4, 35.5, 34.1; IR (neat) 3468, 3026, 2927, 1656, 1588, 1538, 1144 cm^{-1}; HRMS (ESI-TOF) m/z 262.1201 [262.1208 calcd for $C_{16}H_{17}NONa$ $(M + Na)^+$]. Compound *Z*-**7t**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.17−7.32 (m, 6H), 6.81 (ddd, J = 0.7, 2.1, 6.8 Hz, 1H), 6.52 (ddd, J = 0.6, 1.4, 9.2 Hz, 1H), 6.03 (td, J = 1.4, 6.7 Hz, 1H), 5.69−5.77 (m, 1H), 5.43−5.51 (m, 1H), 4.48 (dd, J = 1.6, 7.0 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.52 (app q, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 141.5, 139.4, 136.9, 134.1, 128.9, 128.7, 126.3, 124.8, 121.0, 106.2, 45.3, 35.7, 29.6; IR (neat) 3468, 3026, 2927, 1656, 1588, 1538, 1144 cm^{-1}; HRMS (ESI-TOF) m/z 262.1201 [262.1208 calcd for $C_{16}H_{17}NONa$ $(M + Na)^+$].

1-(2-Pyridonyl)oct-2-yne (7u). Following the general procedure above for the preparation of compound **7f**, 2-propargyloxypyridine **6u**[30] (331 mg, 1.63 mmol) was treated with LiI (109 mg, 0.81 mmol) for 26 h. Purification by column chromatography (SiO_2, ethyl acetate) afforded 270 mg (81% yield) of **7u** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 2.1, 6.9 Hz, 1H), 7.32 (ddd, J = 2.1, 6.6, 9.0 Hz, 1H), 6.55 (app d, J = 9.2 Hz, 1H), 6.21 (dt, J = 1.4, 6.8 Hz, 1H), 4.72 (t, J = 2.3 Hz, 2H), 2.23 (tt, J = 2.3, 7.2 Hz, 2H), 1.53 (pentet, J = 7.2 Hz, 2H), 1.26−1.40 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 139.7, 136.0, 120.6, 106.1, 88.8, 73.0, 38.4, 31.3, 28.3, 22.4, 19.1, 14.2; IR (neat) 3458, 3078, 2932, 2856, 2228, 1659, 1588, 1534, 1462, 1350, 1259, 1142 cm^{-1}; HRMS (ESI-TOF) m/z 204.1390 [204.1388 calcd for $C_{13}H_{18}NO$ $(M + H)^+$].

5-Phenyl-1-(2-pyridonyl)pent-2-yne (7v). Following the general procedure above for the preparation of compound **7f**, 2-propargyloxypyridine **6v**[30] (156 mg, 0.66 mmol) was treated with LiI (65 mg, 0.48 mmol) for 26 h. Purification by column chromatography (SiO_2, 1:1 hexane/ethyl acetate) afforded 133 mg (85% yield) of **7v** as a brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 2.1, 6.9 Hz, 1H), 7.19−7.35 (m, 6H), 6.54 (dt, J = 0.6, 9.2 Hz, 1H), 6.14 (app t, J = 6.6 Hz, 1H), 4.69 (t, J = 2.2 Hz, 2H), 2.85 (t, J = 7.4 Hz, 2H), 2.57 (tt, J = 2.4, 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 140.2, 139.7, 135.9, 128.4, 126.3, 120.2, 106.2, 105.9, 87.6, 73.7, 38.2, 34.6, 20.8; IR (neat) 3028, 2928, 2235, 1667, 1651, 1538, 1454, 1353, 1261, 1145 cm^{-1}; HRMS (ESI-TOF) m/z 260.1044 [260.1051 calcd for $C_{16}H_{15}NONa$ $(M + Na)^+$].

1-Cyclohexyl-3-(2-pyridonyl)prop-1-yne (7w). Following the general procedure above for the preparation of compound **7f**, 2-propargyloxypyridine **6w**[30] (149 mg, 0.69 mmol) was treated with LiI (110 mg, 0.82 mmol) for 26 h. Purification by column chromatography (SiO_2, 1:1 hexane/ethyl acetate) afforded 114 mg (77% yield) of **7w** as a brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 2.2, 7.0 Hz, 1H), 7.33 (ddd, J = 1.6, 8.6, 10.8 Hz, 1H), 6.56 (d, J = 9.1 Hz, 1H), 6.22 (t, J = 6.8 Hz, 1H), 4.74 (d, J = 2.0 Hz, 2H), 2.38−2.46 (m, 1H), 1.77−1.87 (m, 2H), 1.68−1.73 (m, 2H), 1.40−1.54 (m, 3H), 1.25−1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 139.4, 135.6, 120.3, 105.9, 92.7, 72.6, 38.1, 32.4, 29.1, 25.7, 24.8; IR (neat) 2930, 2855, 2235, 1668, 1574, 1538, 1449, 1351, 1258, 1144 cm^{-1}; HRMS (ESI-TOF) m/z 238.1203 [238.1208 calcd for $C_{14}H_{17}NONa$ $(M + Na)^+$].

1-Phenyl-3-(2-pyridonyl)prop-1-yne (7x). Following the general procedure above for the preparation of compound **7f**, 2-propargyloxypyridine **6x**[30] (102 mg, 0.49 mmol) was added to LiI (130 mg, 0.97 mmol) for 26 h. Purification by column chromatography (SiO_2, 1:1 hexane/ethyl acetate) afforded 67 mg (77% yield) of **7x** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 1.8, 6.9 Hz, 1H), 7.48 (app dd, J = 1.6, 7.4 Hz, 2H), 7.40−7.27 (m, 4H), 6.61 (d, J = 9.2 Hz, 1H), 6.27 (dt, J = 1.3, 6.8 Hz, 1H), 5.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 139.9, 136.1, 132.1, 129.1, 128.6, 122.2, 120.8, 106.5, 87.4, 82.2, 38.7; IR (neat) 3072, 3030, 2970, 2235, 1660, 1587, 1538, 1490, 1352, 1146 cm^{-1}; HRMS (ESI-TOF) m/z 232.0731 [232.0738 calcd for $C_{14}H_{11}NONa$ $(M + Na)^+$].

1-((5-Methyl)-2-pyridonyl)oct-2-yne (7z). Following the general procedure above for the preparation of compound **7f**, 2-propargyloxypyridine **6z**[30] (120 mg, 0.55 mmol) was treated with LiI (74 mg, 0.55 mmol) for 26 h. Purification by column chromatography (SiO_2, 1:1 hexane/ethyl acetate) afforded 76 mg (64% yield) of **7z** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (broad s, 1H), 7.16 (dd, J = 2.2, 9.3 Hz, 1H), 6.47 (d, J = 9.1 Hz, 1H), 4.67 (s, 2H), 2.21 (app t, J = 7.1 Hz, 2H), 2.08 (s, 3H), 1.51 (pentet, J = 7.0 Hz, 2H), 1.24−1.39 (m, 4H), 0.88 (app t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 139.6, 130.7, 117.4, 112.4, 85.4, 70.6, 35.4, 28.5, 25.6, 19.6, 16.2, 14.7, 11.4; IR (neat) 2952, 2929, 2861, 2254, 2230, 1673, 1596, 1532, 1461, 1259, 1142 cm^{-1}; HRMS (ESI-TOF) m/z 218.1546 [218.1545 calcd for $C_{14}H_{20}NO$ $(M + H)^+$].

3-Iodo-4-triisopropylsiloxy-2-(2-pyridonyl)but-2-en-1-ol (22bb). LiI (45 mg, 0.33 mmol) was added to 2-propargyloxypyridine **6bb**[30] (107 mg, 0.33 mmol) in a 1 dram screw-top vial, and the reaction was warmed to 100 °C for 26 h. Purification of the residue by column chromatography (SiO_2, 1:1 hexane/ethyl acetate) afforded 24 mg (16% yield) of **22bb** as a white powder: mp 93−95 °C, ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 6.4 Hz,

dx.doi.org/10.1021/jo3015424 | J. Org. Chem. 2012, 77, 8220−8230

1H), 6.55 (d, J = 9.2 Hz, 1H), 6.19 (t, J = 6.6 Hz, 1H), 4.65 (dd, J = 7.2, 13.6 Hz, 1H), 4.37 (dd, J = 4.8, 13.6 Hz, 1H), 4.20 (d, J = 12.2 Hz, 1H), 4.13 (d, J = 12.2 Hz, 1H), 3.72 (app t, J = 6.2 Hz, 1H), 0.94−1.07 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 143.0, 140.8, 138.1, 121.2, 108.2, 106.3, 67.5, 66.7, 17.9, 11.9; IR (neat) 3216, 2941, 2865, 1647, 1571, 1534, 1458, 1284 cm^{-1}; HRMS (ESI-TOF) m/z 486.0932 [486.0938 calcd for $C_{18}H_{30}NO_3ISiNa$ (M + Na)$^+$].

General Procedure for Kinetic Studies Used To Generate the Hammett Plot. To benzyloxypyridine **6a**−**6g** (1.0 equiv) in a 1 dram screw top vial was added LiI (0.5 equiv). The vial was closed and placed in a 90 °C bath. Aliquots were then removed by pipet at appropriate intervals until the reaction reached ∼90% completion, as determined by comparing the benzylic hydrogen resonance of starting material **6** to that of pyridone product **7** using ^{1}H NMR. The initial rate for each trial was determined using the linear segment of each curve.

General Procedure for Crossover Experiments. To pyridine **6q** (1.0 equiv) and pyridine **6b**−**d** (1.0 equiv) in a 1 dram screw top vial was added LiI (1.0 equiv). The vial was closed and heated at 100 °C for 26 h. After cooling, $CDCl_3$ (1.5 mL) was added, and the crude reaction mixture was analyzed by ^{1}H NMR. Benzylic resonances were assigned to compounds **A**−**D** by adding authentic samples of each species to the ^{1}H NMR tube.

General Procedure for Salt Studies. To a solution of pyridine **6j** (1.0 equiv) in CH_3CN (2.0 M) in a 1 dram screw top vial was added a metal salt (3.0 equiv). The vial was closed and heated at 85 °C for 26 h. After cooling, $CDCl_3$ (1.5 mL) was added, and the crude reaction mixture was analyzed by ^{1}H NMR.

2-Benzylthiopyridine (26). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (842 mg, 7.50 mmol) was added to 2-chloropyridine (0.47 mL, 5.00 mmol) and benzyl mercaptan (0.97 mL, 7.50 mmol) in 1,4-dioxane (22.7 mL). After 15 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 914 mg (91% yield) of **26** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (app ddd, J = 1.0, 1.8, 4.9 Hz, 1H), 7.47 (ddd, J = 1.9, 7.4, 9.2 Hz, 1H), 7.39−7.43 (m, 2H), 7.27−7.33 (m, 2H), 7.20−7.25 (m, 1H), 7.16 (dtd, J = 0.4, 1.0, 8.1 Hz, 1H), 6.99 (ddd, J = 1.0, 5.0, 7.4 Hz, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.0, 149.6, 138.2, 136.2, 129.2, 128.7, 217.3, 122.3, 119.8, 34.6; IR (neat) 3063, 3028, 2997, 2927, 1578, 1556, 1453, 1413, 1123 cm^{-1}; HRMS (ESI-TOF) m/z 202.0688 [202.0690 calcd for $C_{12}H_{12}NS$ (M + H)$^+$].

Migration in the Presence of 4-Methyl Benzyl Iodide 28. To pyridine **6a** (1.0 equiv) and 4-methylbenzyl iodide (**28**, 1.0 equiv) in a 1 dram screw top vial was added LiI (0.5 equiv or none). The vial was closed and either heated at 100 °C or maintained at room temperature for 24 h. After cooling, $CDCl_3$ (1.5 mL) was added, and the crude reaction mixture was analyzed by ^{1}H NMR.

2-(α-Deutrobenzyloxy)pyridine (d_1-6a). Following the general procedure outlined above for the synthesis of compound **6r**, potassium *tert*-butoxide (169 mg, 1.51 mmol) was added to 2-chloropyridine (0.10 mL, 1.01 mmol) and α-deutrobenzyl alcohol[34,35] (d_1-**29**, 110 mg, 1.01 mmol) in 1,4-dioxane (4.6 mL). After 22 h, the reaction was worked up and purified by column chromatography (SiO_2, 19:1 hexanes/ethyl acetate) to afford 59 mg (31% yield) of d_1-**6a** as a clear liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (app d, J = 2.8 Hz, 1H), 7.57 (dt, J = 2.1, 8.8 Hz, 1H), 7.43−7.49 (m, 2H), 7.27−7.42 (m, 3H), 6.87 (t, J = 6.5 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 5.36 (app s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 146.8, 138.6, 137.3, 128.4, 128.0, 127.8, 116.9, 111.3, 67.2 (t, J = 89.1 Hz).

(*N*)-(α-Deutrobenzyloxy)-2-pyridone (d_1-7a). Following the general procedure above for the preparation of compound **7f**, 2-(α-deutrobenzyloxy)pyridine (d_1-**6a**, 59 mg, 0.32 mmol) was treated with LiI (21 mg, 0.16 mmol) for 24 h. Purification by column chromatography (SiO_2, 1:1 hexanes/ethyl acetate) afforded 40 mg (68%) of d_1-**7a** as a 1:1 mixture of rotational isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.38 (m, 7H), 6.58 (d, J = 9.2 Hz, 1H), 6.10 (t, J = 6.8 Hz, 1H), 5.09 (app s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 139.42/139.35, 137.2/137.1, 136.3, 128.84/128.82, 128.1, 128.0, 121.3/121.1, 106.24/106.19, 51.7 (t, J = 76.8 Hz)/51.5 (t, J = 79.1 Hz).

(*N*)-(α-Deutrobenzyloxy)-2-thiopyridone (d_1-30). To (*N*)-(α-deutrobenzyloxy)-2-pyridone (d_1-**7a**, 40 mg, 0.22 mmol) in a sealed tube were added P_2S_5 (50 mg, 0.23 mmol) and pyridine (0.65 mL). The tube was sealed and heated at 150 °C for 5 h before cooling and adding H_2O (3 mL) and $CHCl_3$ (6 mL). The phases were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 6 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7:3 hexanes/ethyl acetate) afforded 25 mg (58%) of d_1-**30** as 1:1 mixture of rotational isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.25−7.37 (m, 5H), 7.12 (tt, J = 1.8, 8.8 Hz, 1H), 6.56 (tt, J = 1.4, 6.8 Hz, 1H), 5.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 139.9/139.8, 136.4/136.3, 135.0, 133.7, 129.0 (broad), 128.4 (broad), 113.7/113.5, 105.0, 58.5 (t, J = 78.8 Hz)/58.2 (t, J = 74.4 Hz); IR (neat) 3443, 3033, 2927, 1618, 1532, 1459, 1419, 1267, 1128, 1095 cm^{-1}.

Benzyl (*R*)-Methoxyphenylthioacetate (d_1-32). To (*N*)-(α-deutrobenzyloxy)-2-thiopyridone (d_1-**30**, 25 mg, 0.12 mmol) in benzene (0.43 mL) was added MeI (0.04 mL, 0.62 mmol). The reaction was warmed to reflux for 18 h, cooled, and concentrated *in vacuo*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, J = 5.8 Hz, 1H), 8.42 (t, J = 7.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.70 (t, J = 6.4 Hz, 1H), 7.22−7.34 (m, 5H), 5.91 (s, 1H), 2.83 (s, 3H).

To the crude pyridinium salt was added thiourea (11 mg, 0.15 mmol), and the neat mixture was heated at 160 °C. After 30 min, the reaction was removed from the heat, and 10% (w/v) aq NaOH (1.2 mL) was added. The reaction was then heated to reflux for 3 h. After cooling, the reaction was acidified with 6 M aq HCl and extracted with Et_2O (5 × 6 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Partial purification by column chromatography (SiO_2, 39:1 hexanes/ethyl acetate) afforded 3 mg (17%) of impure d_1-**31**.

To a solution of impure α-deutrobenzyl mercaptan (d_1-**31**, 3 mg, 0.022 mmol) in CH_2Cl_2 (0.3 mL) in a conical vial were added (*R*)-methoxyphenylacetic acid (5 mg, 0.026 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (5 mg, 0.026 mmol), and *N*,*N*-dimethylaminopyridine (3 mg, 0.022 mmol). After 4.5 h, the reaction was washed with H_2O (3 mL), 1 M aq HCl (3 mL), H_2O (3 mL), satd aq $NaHCO_3$ (3 mL), and H_2O (3 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by pipet column (SiO_2, 19:1 hexanes/ethyl acetate) afforded thioester d_1-**32** for ^{1}H NMR analysis: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.38 (m, 10H), 4.70 (s, 1H), 4.02 (s, 0.5H), 3.95 (s, 0.5H), 3.39 (s, 3H).

Benzyl (*R*)-Methoxyphenylthioacetate (32). To a solution of benzyl mercaptan (0.01 mL, 0.073 mmol) in CH_2Cl_2 (1.0 mL) in a conical vial were added (*R*)-methoxyphenylacetic acid (15 mg, 0.088 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl (17 mg, 0.088 mmol) and *N*,*N*-dimethylaminopyridine (9 mg, 0.073 mmol). After 7 h, the reaction was washed with H_2O (3 mL), 1 M aq HCl (3 mL), H_2O (3 mL), satd aq $NaHCO_3$ (3 mL), and H_2O (3 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.44 (m, 2H), 7.28−7.38 (m, 3H), 7.16−7.27 (m, 5H), 4.75 (s, 1H), 4.09 (d, J = 13.7 Hz, 1H), 4.01 (d, J = 13.7 Hz, 1H), 3.44 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds and mechanistic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation under CHE-0911264, awards from Research Corporation for Science Advancement, Arnold and Mabel Beckman Foundation Scholars Program, Donors of the American Chemical Society Petroleum Research Fund, Calvin College, and Pomona College. NMR spectrometers were provided by a Major Research Instrumentation grant of the National Science Foundation under CHE-0922973. We thank Ms. E. Rhude and Mr. N. Romero (Calvin College) and Dr. J. Greaves (UC-Irvine) for their work in support of this project and Drs. C. D. Anderson (Pleotint, LLC), T. Hoye (U of Minnesota), J. Johnson (Hope College), and J. Dinnocenzo (U of Rochester) for helpful conversations regarding this work.

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