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# Copper-Catalyzed Direct *ortho*-Alkylation of *N*-Iminopyridinium Ylides with *N*-Tosylhydrazones

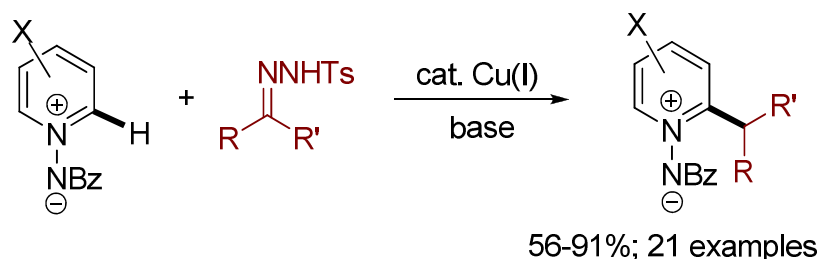
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**ABSTRACT.** Copper-catalyzed cross-coupling of *N*-tosylhydrazones with *N*-iminopyridinium ylides leads to the direct C-H alkylation. This direct C-H bond alkylation transformation use cheap CuI as the catalyst without any ligand. The reaction is operationally simple and under mild conditions, giving the corresponding alkylated pyridines in moderate to good yields. DFT calculation provides insights into the

1 reaction mechanism, suggesting that the reaction proceeds through the Cu carbene migratory insertion  
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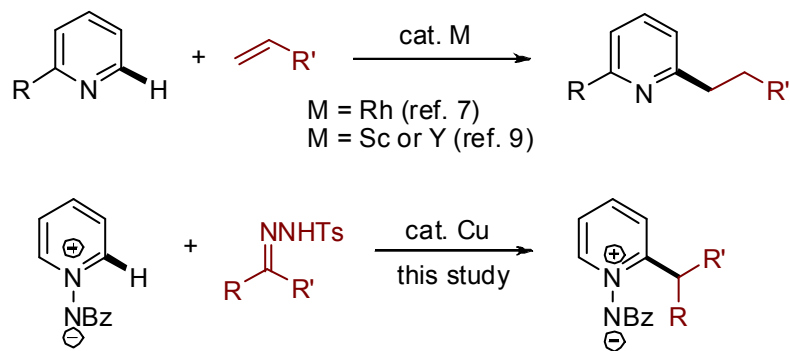
## 5 6 7 INTRODUCTION 8 9

10  
11 Pyridine core is important structure unit which exists widely in various natural products,  
12 pharmaceuticals, ligands, and synthetic building blocks.<sup>1</sup> The development of synthetic methodologies  
13 toward substituted pyridine derivatives, especially through direct C-H functionalization, has attracted  
14 great attentions in recent years.<sup>2-10</sup> Early efforts in this area were focused on C2 lithiation of pyridines,  
15 followed by alkylation.<sup>2a,c,4b</sup> Other strategy involves the reaction of Grignard reagents with pyridine *N*-  
16 oxide as described by Almvist and Olsson.<sup>4c</sup> More recently, transition-metal-catalyzed approach has  
17 become the mainstream of the study. In this context, Fagnou, Charette, Hiyama and other groups have  
18 disclosed their pioneering work on transition-metal-catalyzed *ortho*-arylation or -alkenylation through  
19 C-H functionalization of pyridine *N*-oxides or *N*-iminopyridinium ylides.<sup>5,6</sup> These remarkable progresses  
20 have made 2-aryl and 2-alkenyl pyridine derivatives easily available. In sharp contrast, the  
21 corresponding *ortho*-alkylation of pyridines with similar strategy remains a challenging problem, largely  
22 due to the  $\beta$  hydride elimination of transition metal alkyl species involved in the reaction pathway.  
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40 Recently, Bergman and Ellman have developed an approach toward *ortho*-alkylation of pyridines by  
41 using Rh(I)-phosphine complexes-catalyzed C-H bond addition to olefins.<sup>7,8</sup> Moreover, Hou and  
42 coworkers have reported that half-sandwich rare-earth dialkyl complexes and B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> can serve as  
43 excellent catalyst system for similar transformations (Scheme 1).<sup>9,10</sup> Although significant breakthrough  
44 has been made for *ortho*-alkylation of pyridines, some drawbacks still remain. First, both reactions  
45 require expensive and/or complicated catalyst systems. Besides, the regioselectivity is a problem in the  
46 reaction with substituted olefins. Thus, the development of more general method for highly selective  
47 *ortho*-alkylation of pyridines, ideally by using simple and inexpensive metal catalysts, is highly  
48 demanded.  
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We have recently reported a series of Cu-catalyzed cross-coupling reactions using *N*-tosylhydrazones as coupling partners.<sup>11</sup> These reactions presumably proceed through migratory insertion process of the Cu-carbene intermediate.<sup>12</sup> As a continuation of our interest in this area, herein we report the first Cu-catalyzed direct alkylation of *N*-iminopyridinium ylides<sup>6,13</sup> with *N*-tosylhydrazones and inexpensive CuI as the catalyst. The reaction represents an efficient and highly selective approach toward both primary and secondary *ortho*-alkyl-substituted pyridine derivatives (Scheme 1).

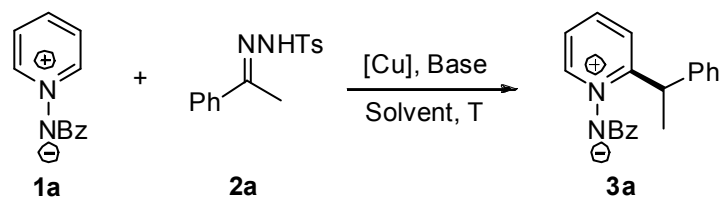
**Scheme 1.** Transition-Metal-Catalyzed *ortho*-Alkylation of Pyridines



## RESULTS AND DISCUSSIONS

Based on the reports by Charette and coworkers,<sup>6</sup> we employed *N*-iminopyridinium ylide **1a** as the substrate and studied its reaction with *N*-tosylhydrazones **2a** (Table 1). After some initial experiments (Table 1, entries 1-6), we observed that in the presence of LiOtBu in toluene,<sup>14</sup> Cu-catalyzed coupling of **1a** and **2a** could afford 2-alkyl substituted pyridine **3a** in 66% isolated yield (Table 1, entry 3). Encouraged by these initial results, we proceeded to optimize the reaction conditions by screening the temperature and copper salts (Table 1, entries 7-10). We found that the initially used CuI provided better results as compared with other Cu salts. We then went on to screen other reaction parameters and observed that the reaction was significantly affected by the copper catalyst loading and the ratio of substrates. The optimal yield could be achieved by using 20 mol% of the CuI catalyst and LiOtBu (3.5 equiv) in toluene, and the ratio of pyridinium ylide to *N*-tosylhydrazone is 1:2 (Table 1, entry 11).

**Table 1.** Optimization of the Reaction Conditions<sup>a</sup>



entry	CuX (mol%)	base	solvent	$T(^{\circ}\text{C})$	yield (%) <sup>b</sup>
1	CuI (10)	LiOtBu	dioxane	90	30
2	CuI (10)	LiOtBu	DCE	90	34
3	CuI (10)	LiOtBu	PhMe	90	66
4	CuI (10)	NaOtBu	PhMe	90	22
5	CuI (10)	$\text{Cs}_2\text{CO}_3$	PhMe	90	31
6	CuI (10)	$\text{K}_2\text{CO}_3$	PhMe	90	24
7	CuI (10)	LiOtBu	PhMe	110	53
8	CuI (10)	LiOtBu	PhMe	80	23
9	CuBr (10)	LiOtBu	PhMe	90	55
10	CuCl (10)	LiOtBu	PhMe	90	45
11 <sup>c</sup>	CuI (20)	LiOtBu	PhMe	90	81

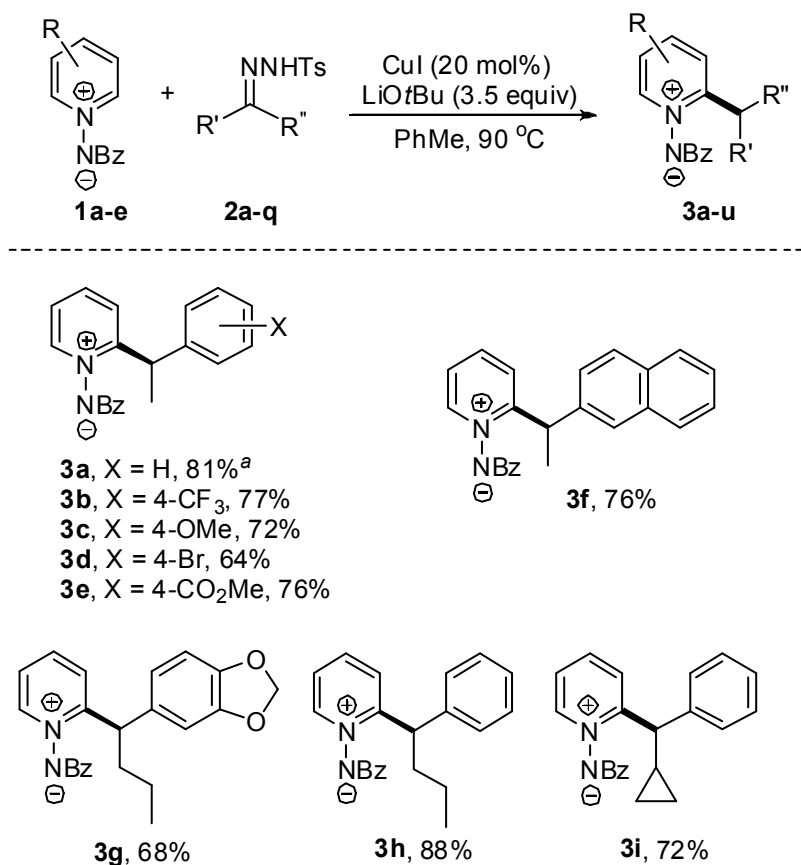
<sup>a</sup> Reactions were carried out with pyridinium ylides (0.4 mmol), *N*-tosylhydrazones (0.6 mmol) and base (1.2 mmol) in solvent (2 mL) for 5 h, unless otherwise noted. <sup>b</sup> Isolated yield. <sup>c</sup> The reaction was carried out with 0.8 mmol *N*-tosylhydrazone and 1.4 mmol LiOtBu.

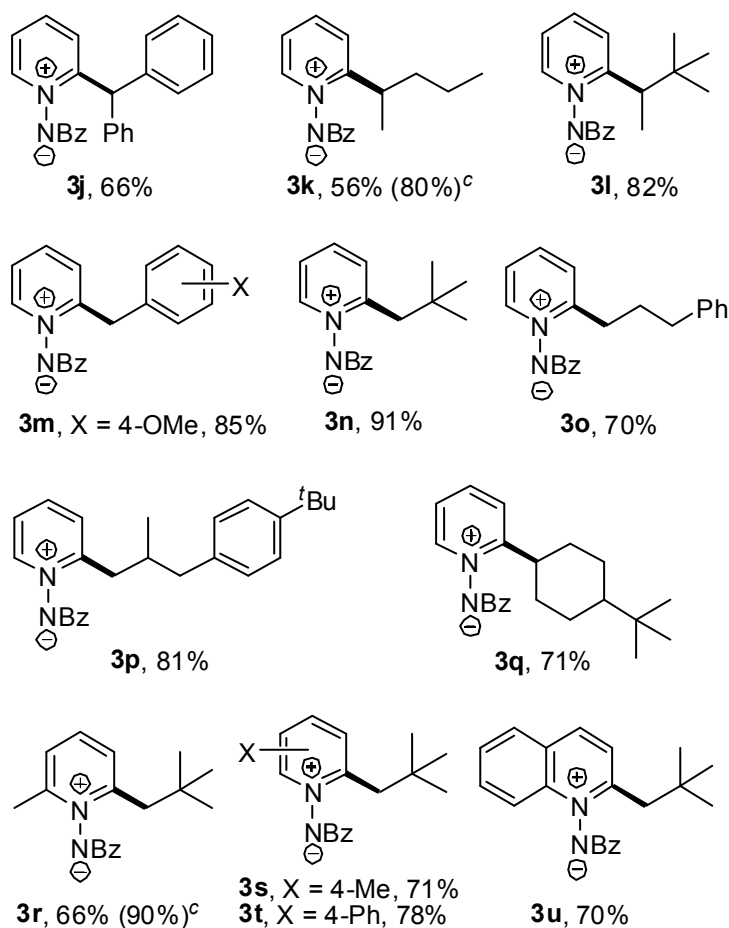
With the optimized reaction conditions in hand, the scope of this transformation was explored by using various pyridinium ylides and *N*-tosylhydrazones. Treatment of pyridinium ylide **1a** with a series of *N*-tosylhydrazones **2a–q** furnished the corresponding products **3a–q** in moderate to good yields (Scheme 2). The reaction was not significantly affected by the substituents on the aromatic ring of the tosylhydrazones. Both electron-rich (Scheme 2, **3b**, **c**, **g**, **n**) and electron-deficient aryl-substituted tosylhydrazones (Scheme 2, **3b–e**) were effective. Notably, alkoxy, cyclopropyl, ester, bromo groups are

all tolerated under the given reaction conditions. Besides, the reaction also worked well with tosylhydrazones generated from alkyl aldehydes or ketones (Scheme 2, **3k, l, p-u**).

Next, the scope of *N*-iminopyridinium ylide was investigated. The reaction was examined with *N*-iminopyridinium ylides **1b–e**, which were treated with tosylhydrazones **2n** ( $R' = \text{H}$ ,  $R'' = t\text{Bu}$ ) under the optimized reaction conditions. *N*-Iminopyridinium species with substituents at the 2-, and 4-positions underwent the alkylation reaction smoothly and provided the corresponding *ortho* alkylated products in moderate to good yields (Scheme 2, **3r–t**). Notably, this reaction could also be applied to other similar structures. For example, the reaction with *N*-iminoquinolinium afforded the alkylated product in good yield (Scheme 2, **3u**). Finally, it is noteworthy that in all cases, 2,6-dialkylated products were not detected.

**Scheme 2.** Direct Alkylation of *N*-Iminopyridinium Ylides with *N*-Tosylhydrazones<sup>a</sup>



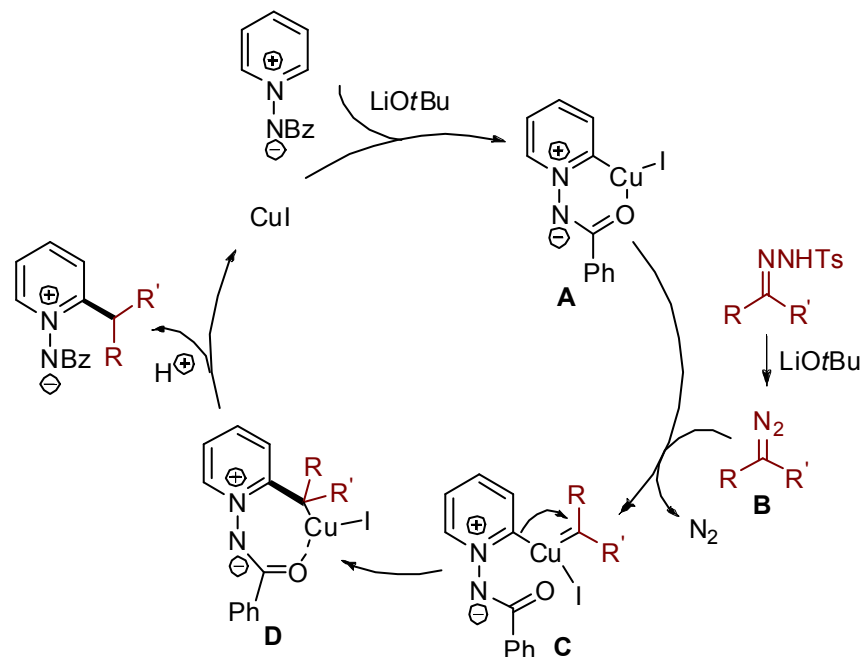


<sup>a</sup> Reaction conditions if not otherwise noted: **1a-e** (0.3 mmol), **2a-q** (0.6 mmol), CuI (20 mol %), LiOtBu (1.05 mmol), PhMe (2 mL), 5-8 h. <sup>b</sup> Isolated yield. <sup>c</sup> The yields in parentheses are these based on recovered starting materials.

Based on our understanding of the copper-catalyzed cross-coupling reaction of *N*-tosylhydrazones, a plausible mechanism proposed for this novel direct C-H bond alkylation has been depicted in Scheme 3.<sup>6c,11</sup> The key step in the reaction is proposed to be the migratory insertion of Cu carbene species. In the presence of base and Cu(I) salt, the copper pyridinium ylides **A** is formed *via* direct C-H activation. The reaction of copper pyridinium ylides **A** with diazo substrate **B**, which is generated *in situ* from *N*-tosylhydrazone in the presence of base, leads to the formation of copper-carbene species **C**. Migratory insertion of alkynyl group to the carbenic carbon gives intermediate **D**.

Finally, the alkylated product is formed by protonation of intermediate **D**, in conjunction with the regeneration of the Cu(I) catalyst.

### Scheme 3. Mechanistic Rationale



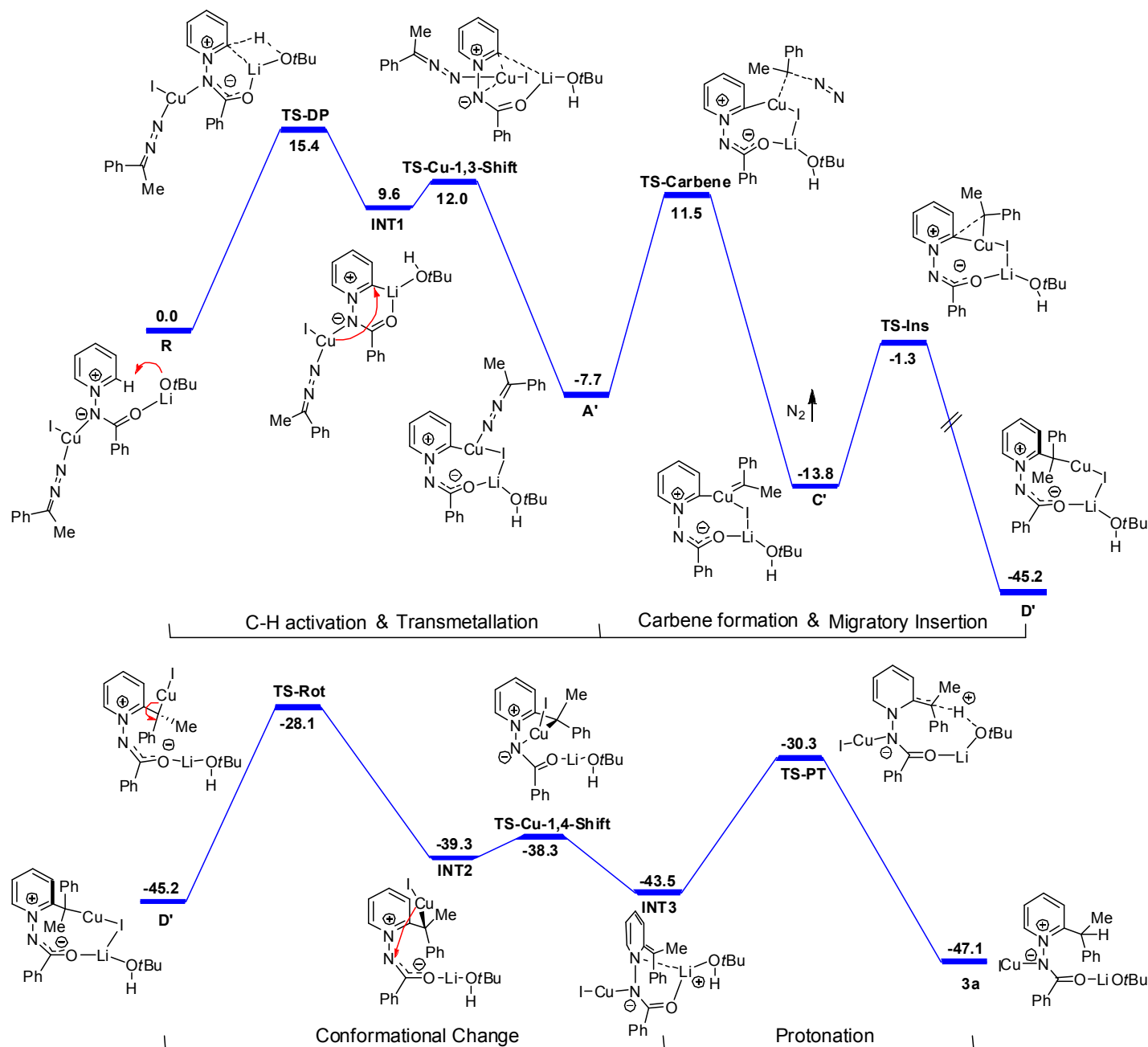
To have a better understanding of the reaction mechanism, density functional theory (DFT)<sup>15</sup> studies have been performed with Gaussian 09 program<sup>16</sup> using B3LYP<sup>17</sup> method. Based on an extensive computational study on many possible mechanisms, the whole reaction pathway was obtained.<sup>18</sup> For C, H, O, N and Li, the 6-311+G\*\* basis set was used. For Cu and I, the SDD<sup>19</sup> basis set with Effective Core Potential (ECP) was used. The structures were optimized with SMD<sup>20</sup> method in toluene ( $\epsilon=2.374$ ). Harmonic vibration frequency calculations confirmed that the optimized structures are either minima (having no imaginary vibration) or transition states (having one imaginary vibration).

As shown in Scheme 4, from the reactant complex **R**, the deprotonation occurs *via* the transition state **TS-DP** (15.4 kcal/mol), leading to **INT1** (9.6 kcal/mol). Then, a Cu-Li exchange happened *via* the 1,3-Cu shift transition state **TS-Cu-1,3-Shift** over a small barrier of 2.4 kcal/mol, leading to the copper pyridinium ylide **A'**. Subsequently, the copper-carbene species **C'** formed *via* transition state **TS-Carbene** over a barrier of 19.2 kcal/mol, releasing a nitrogen molecule. In **C'**, migratory insertion of the



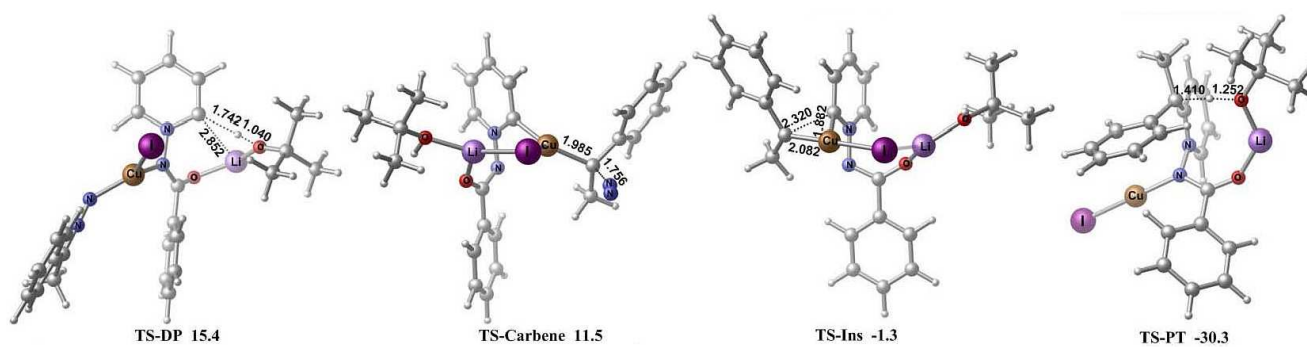
alkynyl group to the carbenic carbon *via* transition state **TS-Ins** leading to intermediate **D'**. After a C-C single bond rotation (**TS-Rot**) and 1,4-Cu shift (**TS-Cu-1,4-Shift**), another conformation of **D'**, **INT3** is

**Scheme 4.** The Calculated Full Reaction Pathway. The relative free energies in solvent  $\Delta G_{\text{sol}}$  are in kcal/mol, calculated at B3LYP/6-311+G\*\*/SDD level

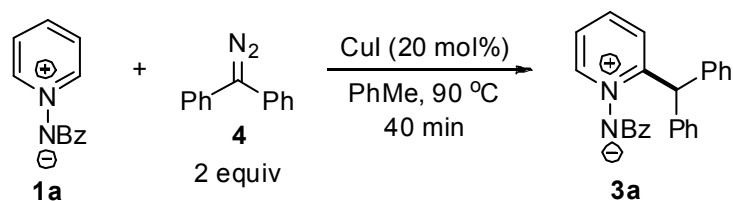


generated. Then the protonation of **INT3** by HO*t*Bu occurs *via* transition state **TS-PT** over a barrier of 13.2 kcal/mol, leading to the final product **3a** and regenerating the Cu(I) catalyst. For transition states **TS-DP** and **TS-Carbene**, the *N*-coordinated structures are also calculated and shown to be unfavorable.<sup>18</sup> The key transition states along the reaction coordinate are shown in Figure 1.

**Figure 1.** The Optimized Important Transition States on the Full Reaction Pathways. Bond lengths are in Å and relative free energies in solvent  $\Delta G_{\text{sol}}$  are in kcal/mol, calculated at B3LYP/6-311+G\*\*/SDD level.



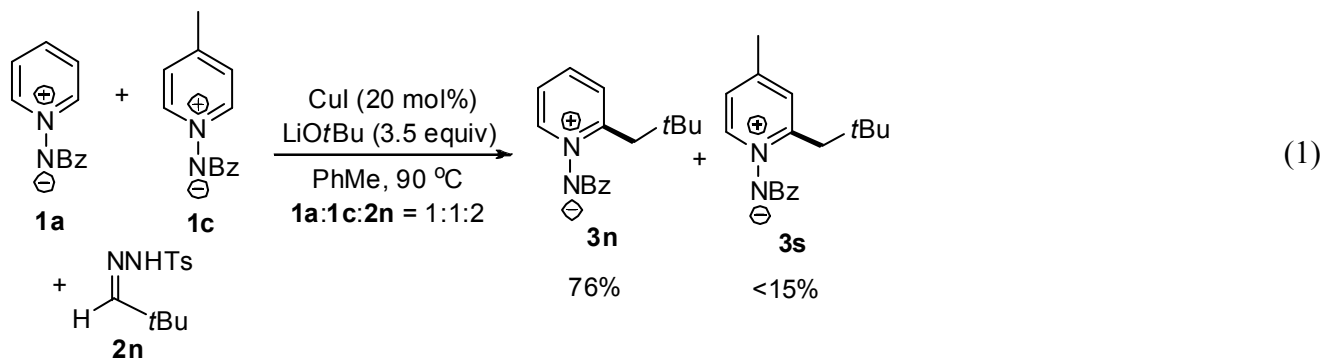
The results of DFT calculation is generally in accordance with the simplified mechanistic rationale depicted in Scheme 3, although the DFT calculation indicates the initial deprotonation and the last protonation steps require the participation of lithium. However, it should be mentioned that an alternative mechanism which involves a direct Cu carbene insertion into C-H bond of heterocycles cannot be strictly eliminated.<sup>21</sup> To verify such possible pathway, a control experiment has been carried out. Thus, diphenyldiazomethane **4** was prepared and was submitted to CuI-catalyzed reaction with *N*-iminopyridinium ylide **1a** (Scheme 5). In the absence of base, only trace product could be identified, while the expected product **3a** could be isolated in 58% yield in the presence of the base. For metal carbene C-H insertion base is not needed, therefore, these results do not support a direct Cu carbene C-H insertion mechanism. DFT calculation also suggests that Cu carbene C-H insertion mechanism can be ruled out due to unfavorable energy barrier.<sup>18</sup>

**Scheme 5.** Control experiments with diphenyldiazomethane **4**.

Base	Yield
none	trace
LiOtBu (1.5 equiv)	58%

Charette and coworkers have carried out deuterium exchange experiments in their Cu-catalyzed *ortho*-alkenylation of *N*-iminopyridinium ylides.<sup>6c</sup> The study indicates that deprotonation occurs at the 2,6-positions of the pyridinium ring in the presence of CuBr<sub>2</sub> (10 mol%) and K<sub>2</sub>CO<sub>3</sub> (2 equiv). Our deuterium exchange experiments also suggest preferential deprotonation at 2,6-positions in the presence of CuI (20 mol%) and LiOtBu (3.5 equiv). Furthermore, DFT calculation shows protons at 2,6-positions of pyridinium ring are more acidic than those at 3,4-positions.<sup>18</sup>

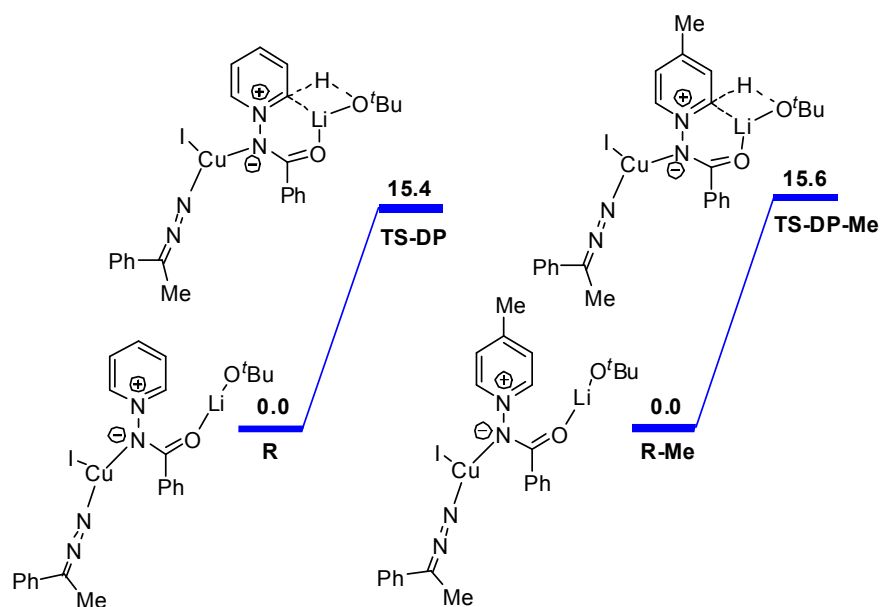
To gain further insights, the effect of substituents on the reaction was studied (eq 1). The competition experiment of *N*-iminopyridinium ylides **1a** and **1c** in the reaction with *N*-tosylhydrazone **2n** shows that **1a** is more reactive than **1c**.



The calculated pathways show that the deprotonation step is irreversible. Therefore, the barriers of the deprotonation step can affect the ratio of **3n** and **3s**. Thus, the barriers of the deprotonation step of **1a**

and **1c** were calculated. The results show that the barrier of **1c** is 0.2 kcal/mol in  $\Delta G_{\text{sol}}$  (1.0 kcal/mol in  $\Delta E_{\text{sol}}$ ) higher than that of **1a**, which qualitatively agrees with the experimental results (Scheme 6). This result can be rationalized by the fact that electron-donation of the methyl group makes the pyridine ring more electronic rich, which is unfavorable for the deprotonation.

**Scheme 6.** Calculation on Substituent Effects. The relative free energies in solvent  $\Delta G_{\text{sol}}$  are in kcal/mol, calculated at B3LYP/6-311+G\*\*/SDD level.



## CONCLUSION

In this paper, we have reported an efficient cross-coupling of *N*-iminopyridinium ylides with *N*-tosylhydrazones through direct C-H bond functionalization by using cheap CuI as the catalyst without adding ligand. This direct C-H bond alkylation transformation, which is operationally simple and under mild conditions, affords the corresponding alkylated pyridines in moderate to good yields. Since *N*-tosylhydrazones are easily prepared from the corresponding aldehydes or ketones, this reaction represents a practical access toward various 2-alkyl pyridines. Computational study provides insights into the reaction mechanism, in particular the deprotonation and the Cu carbene migratory insertion

processes. This information is useful for the further development of C-H bond functionalization based on Cu carbene transformations.

## EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere in a flame-dried reaction flask. All solvents were distilled prior to use. Toluene and dioxane were dried over Na with benzophenone-ketyl intermediate as indicator. DCE was dried over CaH<sub>2</sub>. 200-300 Mesh silica gel was used for the chromatography. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded in ppm using tetramethylsilane (TMS) as the internal standard. IR spectra are reported in wave numbers, cm<sup>-1</sup>. For HRMS measurements, the mass analyzer is FT-ICR.

*The preparation of N-tosylhydrazones (2a-q).* The literature procedure was followed.<sup>11</sup> A solution of pure TsNHNH<sub>2</sub> (5 mmol) in methanol (5 mL) was stirred and heated to 60 °C until the TsNHNH<sub>2</sub> dissolved. The mixture was cooled to room temperature. Then carbonyl compounds were dropped into the mixture slowly. After approximately 5 minutes the crude products could be obtained as solid precipitations. The precipitations were washed by Petroleum ether then removed in *vacuo* to give the pure products. In general the yields were around 95%. Because of the relatively low activity of diaryl-substituted ketones, their reactions at room temperature may be incomplete. They should be reacted in refluxing methanol for approximately 1 h. The reaction could be monitored by TLC.

*The preparation of N-iminopyridinium ylides (1a-e).* Literature procedure was followed.<sup>6</sup> Pyridine (0.100 mL, 1.24 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine (272 mg, 1.36 mmol) were added to H<sub>2</sub>O/THF (1:1 mixture, 1.0 mL). The reaction flask was sealed with a septum, and the resulting suspension was stirred at 40 °C for 16 h. During this period, the reaction mixture turned dark red. The reaction was poured into aqueous NaOH (2.5 N, 6 mL) at room temperature, stirred for 5 min, and then benzoyl chloride (0.215 mL, 1.84 mmol) was added in one portion. After 5 h, the reaction was diluted with H<sub>2</sub>O (5 mL) and extracted with CHCl<sub>3</sub> (3x10 mL). The combined organic phases were washed with

NaOH (2.5 N, 5 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure affording the *N*-iminopyridinium ylides **1a-e**. The <sup>1</sup>H NMR spectra data of **1a-e** were found consistent with those previously reported in the literature.<sup>6</sup>

*Typical procedure for the reaction between N-iminopyridinium ylides and N-tosylhydrazones.* Under a nitrogen atmosphere, *N*-iminobenzoylpyridinium ylide (**1a**, 59.4 mg, 0.3 mmol) and 4-methyl-*N'*-(1-phenylethylidene)benzenesulfonohydrazide (**2a**, 172.8 mg, 0.6 mmol) were added to a mixture of CuI (11.5 mg, 0.06 mmol), LiOtBu (84.0 mg, 1.05 mmol) in PhMe (2 mL). The mixture was then stirred at 90 °C for 6 h. The reaction could be monitored with TLC. Upon completion of the reaction, the solvent was removed in *vacuo*, and the crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 40:1) to afford pure **3a** as a yellow oil (73 mg, 81%).

*Benzoyl(2-(1-phenylethyl)pyridinium-1-yl)amide (3a).*<sup>6b</sup> (73 mg, 81%); *R<sub>f</sub>* = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 40:1), brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.64 (d, *J* = 6.0 Hz, 1H), 8.19 (dd, *J* = 1.6 Hz, 7.2 Hz, 2H), 7.82 (t, *J* = 7.2 Hz, 1H), 7.49-7.42 (m, 5H), 7.35-7.24 (m, 5H), 5.23 (q, *J* = 7.2 Hz, 1H), 1.70 (d, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.0, 160.2, 145.6, 141.1, 137.3, 137.2, 130.0, 128.8, 128.1, 128.0, 127.8, 127.2, 125.5, 123.1, 39.6, 19.1.

*Benzoyl(2-(1-(4-(trifluoromethyl)phenyl)ethyl)pyridinium-1-yl)amide (3b).*<sup>6b</sup> (85 mg, 77%); *R<sub>f</sub>* = 0.4 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 30:1), brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.67 (d, *J* = 1.2 Hz, 1H), 8.13 (d, *J* = 6.4 Hz, 2H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.57-7.49 (m, 4H), 7.43-7.37 (m, 5H), 5.23 (q, *J* = 6.8 Hz, 1H), 1.71 (d, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.7, 159.7, 146.9, 146.2, 138.3, 137.8, 131.0, 130.2 (q, *J* = 32 Hz), 129.2, 128.9, 128.7, 126.5, 126.1, 124.5, 121.1 (q, *J* = 272 Hz), 40.6, 20.2.

*Benzoyl(2-(1-(4-methoxyphenyl)ethyl)pyridinium-1-yl)amide (3c).*<sup>6b</sup> (72 mg, 72%); *R<sub>f</sub>* = 0.35 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 40:1), brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.64 (d, *J* = 6.0 Hz, 1H), 8.21 (d, *J* = 6.0 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.49-7.41 (m, 5H), 7.23 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.19 (q,

$J = 7.2$  Hz, 1H), 3.79 (s, 3H), 1.67 (d,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 161.6, 159.6, 146.5, 138.1, 134.0, 130.9, 130.0, 129.0, 128.7, 126.3, 123.9, 115.0, 56.1, 39.7, 19.9.

*Benzoyl(2-(1-(4-bromophenyl)ethyl)pyridinium-1-yl)amide (3d)*. (73 mg, 64%);  $R_f = 0.3$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 40:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (d,  $J = 4.8$  Hz, 1H), 8.16 (d,  $J = 6.4$  Hz, 2H), 7.84 (t,  $J = 7.6$  Hz, 1H), 7.51-7.48 (m, 2H), 7.45-7.42 (m, 5H), 7.16-7.14 (m, 2H), 5.14 (q,  $J = 7.2$  Hz, 1H), 1.66 (d,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 159.5, 145.9, 140.3, 137.5, 137.1, 131.9, 130.2, 129.7, 128.1, 127.9, 125.3, 123.5, 121.3, 39.3, 19.1; FTIR (film) 3342.0, 2973.3, 2890, 1593.6, 1554.9, 1487.1, 1330.8  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 382.1 (21), 381.1 [(M+H) $^+$ , 100], 380.1 (21), 379.1 (99), 281.5 (3), 190.5 (5); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{20}\text{H}_{18}\text{BrN}_2\text{O}$  (M+H) $^+$  381.0597, found 381.0603.

*Benzoyl(2-(1-(4-(methoxycarbonyl)phenyl)ethyl)pyridinium-1-yl)amide (3e)*.<sup>6b</sup> (82 mg, 76%);  $R_f = 0.3$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.69 (d,  $J = 6.0$  Hz, 1H), 8.16 (t,  $J = 6.0$  Hz, 2H), 7.99 (d,  $J = 8.4$  Hz, 1H), 7.94 (d,  $J = 8.4$  Hz, 1H), 7.86 (q,  $J = 6.0$  Hz, 1H), 7.54-7.50 (m, 1H), 7.46-7.42 (m, 4H), 7.35 (d,  $J = 8.4$  Hz, 2H), 5.25 (q,  $J = 6.8$  Hz, 1H), 3.90 (s, 3H), 1.71 (d,  $J = 7.2$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 166.7, 159.1, 146.4, 145.9, 137.3, 137.0, 130.10, 130.00, 129.1, 128.0, 128.0, 127.8, 125.3, 123.5, 52.1, 39.3, 19.1.

*Benzoyl(2-(1-(naphthalen-2-yl)ethyl)pyridinium-1-yl)amide (3f)*. (80 mg, 76%);  $R_f = 0.3$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 30:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 (br, 1H), 8.21 (d,  $J = 6.0$  Hz, 2H), 7.78 (m, 5H), 7.43-7.35 (m, 8H), 5.35 (d,  $J = 3.6$  Hz, 1H), 1.78 (d,  $J = 6.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 160.2, 145.7, 138.6, 137.6, 137.2, 133.4, 132.6, 130.2, 128.6, 128.2, 127.9, 127.8, 126.7, 126.6, 126.4, 126.1, 125.8, 123.4, 39.9, 18.9; FTIR (film) 3068.7, 2975.3, 2878.2, 1682.1, 1555.5, 1488.6, 1330.8  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 354.2 (26), 353.2 [(M+H) $^+$ , 100], 335.2 (7), 176.6 (3); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}$  (M+H) $^+$  353.1648, found 353.1648.

(2-(1-(Benzo[d][1,3]dioxol-5-yl)butyl)pyridinium-1-yl)(benzoyl)amide (**3g**). (76 mg, 68%);  $R_f$  = 0.35 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 20:1), brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.49 (br, 1H), 8.13 (br, 2H), 7.72 (m, 1H), 7.45-7.24 (m, 5H), 6.71-6.50 (m, 3H), 5.81 (s, 2H), 4.92 (br, 1H), 1.90 (m, 2H), 1.10 (m, 2H), 0.78 (t,  $J$  = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  169.8, 159.2, 148.0, 146.7, 145.8, 137.4, 137.3, 133.3, 130.0, 128.0, 127.8, 125.2, 123.1, 122.0, 108.9, 108.5, 101.1, 44.4, 35.8, 20.6, 13.8; FTIR (film) 2980.0, 2927.7, 2850, 1593.8, 1555.0, 1486.6, 1442.0, 1331.5 cm<sup>-1</sup>; ESI-MS ( $m/z$ , relative intensity): 375.2 [(M+H)<sup>+</sup>, 100], 310.7 (3), 167.6 (8), 177.1 (5); HRMS (ESI)  $m/e$  calcd for C<sub>23</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup> 375.1703, found 375.1709.

Benzoyl(2-(1-phenylbutyl)pyridinium-1-yl)amide (**3h**). (87 mg, 88%);  $R_f$  = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 40:1), brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.50 (d,  $J$  = 5.2 Hz, 1H), 8.14 (d,  $J$  = 3.2 Hz, 2H), 7.72 (t,  $J$  = 7.4 Hz, 1H), 7.44-7.40 (m, 1H), 7.34-7.30 (m, 4H), 7.23-7.18 (m, 4H), 7.14 (m, 1H), 5.02 (t,  $J$  = 7.2 Hz, 1H), 2.26 (m, 2H), 1.23 (m, 2H), 0.79 (t,  $J$  = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.0, 158.2, 144.8, 138.6, 136.3, 129.0, 127.8, 127.6, 127.0, 126.8, 126.3, 124.4, 122.0, 43.8, 34.7, 19.7, 12.8; FTIR (film) 3061.3, 2959.1, 2931.4, 2872.4, 1681.1, 1556.1, 1330.9 cm<sup>-1</sup>; ESI-MS ( $m/z$ , relative intensity): 331.2 [(M+H)<sup>+</sup>, 100], 176.6 (5), 165.6 (3); HRMS (ESI)  $m/e$  calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O (M+H)<sup>+</sup> 331.1805, found 331.1805.

Benzoyl(2-(cyclopropyl(phenyl)methyl)pyridinium-1-yl)amide (**3i**). (71 mg, 72%);  $R_f$  = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 20:1), brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.64 (d,  $J$  = 5.6 Hz, 1H), 8.07 (d,  $J$  = 7.2 Hz, 2H), 7.90 (m, 2H), 7.44-7.38 (m, 4H), 7.36-7.26 (m, 5H), 4.35 (d,  $J$  = 9.6 Hz, 1H), 0.87 (m, 1H), 0.76-0.64 (m, 2H), 0.52-0.40 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.1, 159.0, 145.8, 140.2, 137.0, 130.0, 128.6, 128.2, 128.0, 127.7, 127.4, 127.1, 126.3, 123.3, 50.0, 15.7, 5.8; FTIR (film) 3065.6, 2988.1, 2935.4, 2872.0, 1680.1, 1556.1, 1330.8 cm<sup>-1</sup>; ESI-MS ( $m/z$ , relative intensity): 329.2 [(M+H)<sup>+</sup>, 100], 165.6 (3); HRMS (ESI)  $m/e$  calcd for C<sub>22</sub>H<sub>21</sub>N<sub>2</sub>O (M+H)<sup>+</sup> 329.1654, found 329.1655.

(2-Benzhydrylpyridinium-1-yl)(benzoyl)amide (**3j**).<sup>6b</sup> (72 mg, 66%);  $R_f$  = 0.35 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 20:1), brown oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.79 (d,  $J$  = 5.2 Hz, 1H), 7.99 (d,  $J$  = 6.8 Hz, 1H), 7.81 (t,  $J$  =



7.2 Hz, 1H), 7.54 (d,  $J = 6.0$  Hz, 1H), 7.39-7.28 (m, 10H), 7.11-7.10 (m, 4H), 6.42 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.3, 157.5, 145.8, 139.2, 137.1, 136.5, 129.9, 129.2, 128.7, 127.9, 127.6, 127.6, 127.3, 123.5, 52.1.

*Benzoyl(2-(pentan-2-yl)pyridinium-1-yl)amide (3k)*. (45 mg, 56%);  $R_f = 0.3$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 30:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.55 (br, 1H), 8.19 (br, 2H), 7.88 (br, 1H), 7.58 (m, 1H), 7.52-7.30 (m, 4H), 3.88 (m, 1H), 1.73-1.54 (m, 2H), 1.30 (m, 5H), 0.89 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 161.7, 145.8, 137.9, 137.2, 130.0, 128.0, 127.8, 124.1, 122.9, 37.7, 33.8, 20.3, 19.0, 13.9; FTIR (film) 2950.0, 2916.6, 2800.0, 1593.4, 1553.2, 1490.3, 1334.8  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 269.2  $[(\text{M}+\text{H})^+]$ , 100], 221.2 (15), 134.6 (7), 105.0 (5); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$   $(\text{M}+\text{H})^+$  269.1648, found 269.1649.

*Benzoyl(2-(3,3-dimethylbutan-2-yl)pyridinium-1-yl)amide (3l)*. (69 mg, 82%);  $R_f = 0.3$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (d,  $J = 5.2$  Hz, 1H), 8.20 (d,  $J = 4.0$  Hz, 2H), 7.85 (t,  $J = 7.6$  Hz, 1H), 7.58 (m, 1H), 7.50-7.42 (m, 4H), 4.18 (q,  $J = 7.2$  Hz, 1H), 1.28 (d,  $J = 7.2$  Hz, 3H), 0.96 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.7, 160.3, 145.7, 137.6, 136.4, 129.9, 127.9, 127.8, 125.9, 122.7, 41.4, 35.2, 27.5, 15.6; FTIR (film) 3062.6, 2965.7, 2871.2, 1594.3, 1556.0, 1488.9, 1329.1  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 283.2  $[(\text{M}+\text{H})^+]$ , 100], 195.8 (8), 141.6 (5), 99.3 (3); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}$   $(\text{M}+\text{H})^+$  283.1805, found 283.1806.

*Benzoyl(2-(4-methoxybenzyl)pyridinium-1-yl)amide (3m)*.<sup>6b</sup> (81 mg, 85%);  $R_f = 0.4$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.67 (d,  $J = 6.0$  Hz, 1H), 8.22 (dd,  $J = 1.6$  Hz, 7.2 Hz, 2H), 7.79 (t,  $J = 4.04$  Hz, 1H), 7.53-7.49 (m, 2H), 7.45-7.43 (m, 3H), 7.19-7.17 (m, 2H), 6.91-6.89 (m, 2H), 4.39 (s, 2H), 3.81 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 158.9, 156.6, 144.9, 137.2, 137.0, 130.9, 130.0, 127.9, 127.8, 126.9, 126.6, 123.3, 114.4, 55.2, 36.7.

*Benzoyl(2-neopentylpyridinium-1-yl)amide (3n)*. (73 mg, 91%);  $R_f = 0.3$  ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (d,  $J = 6.0$  Hz, 1H), 8.24-8.19 (m, 2H), 7.81 (t,  $J = 7.6$  Hz, 1H),

7.53-7.47 (m, 2H), 7.44-7.42 (m, 3H), 3.15 (s, 2H), 1.03 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.6, 154.6, 146.2, 137.5, 136.0, 129.9, 128.8, 128.0, 127.8, 123.2, 43.9, 33.9, 29.8; FTIR (film) 3058.6, 2975.7, 2881.2, 1596.3, 1558.0, 1488.9, 1329.1  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 269.2  $[(\text{M}+\text{H})^+]$ , 100], 169.6 (8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}$   $(\text{M}+\text{H})^+$  269.1648, found 269.1652.

*Benzoyl(2-(3-phenylpropyl)pyridinium-1-yl)amide (3o)*. (66 mg, 70%);  $R_f$  = 0.3 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 30:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (br, 1H), 8.17 (m, 2H), 7.73 (br, 1H), 7.42-7.22 (br, 5H), 7.20-7.11 (m, 5H), 3.06 (t,  $J$  = 6.8 Hz, 2H), 2.70-2.66 (m, 2H), 2.07 (t,  $J$  = 6 Hz, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 156.5, 145.7, 141.0, 137.4, 137.3, 130.0, 128.5, 128.4, 128.1, 127.9, 126.5, 126.1, 123.4, 35.5, 31.8, 28.6; FTIR (film) 3070.0, 3030.0, 2925.6, 2830, 1593.8, 1554.8, 1492.1, 1330.8  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 317.2  $[(\text{M}+\text{H})^+]$ , 100], 158.6 (8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}$   $(\text{M}+\text{H})^+$  317.1648, found 317.1649.

*Benzoyl(2-(3-(4-tert-butylphenyl)-2-methylpropyl)pyridinium-1-yl)amide (3p)*. (94 mg, 81%);  $R_f$  = 0.25 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 40:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.59 (br, 1H), 8.20 (br, 2H), 7.72 (br, 1H), 7.44 (m, 5H), 7.16 (m, 2H), 7.00 (m, 2H), 4.10 (m, 1H), 2.81-2.76 (m, 2H), 2.57-2.54 (m, 2H), 1.26 (s, 9H), 0.89 (d,  $J$  = 4.8 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 155.9, 148.8, 145.0, 137.4, 136.7, 130.0, 128.8, 128.1, 128.0, 127.8, 125.1, 123.3, 43.4, 39.8, 34.3, 33.1, 31.4, 19.8; FTIR (film) 2962.5, 2929.8, 2902.9, 2212.8, 1594.2, 1552.9, 1340.1  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 387.2  $[(\text{M}+\text{H})^+]$ , 100], 193.6 (5), 141.6 (8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}$   $(\text{M}+\text{H})^+$  387.2431, found 387.2434.

*Benzoyl(2-(4-tert-butylcyclohexyl)pyridinium-1-yl)amide (3q)*. (71 mg, 71%);  $R_f$  = 0.3 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (br, 1H), 8.20 (br, 2H), 7.89 (t,  $J$  = 6.8 Hz, 1H), 7.55 (m, 1H), 7.48-7.44 (m, 4H), 3.62-3.45 (m, 1H), 2.19 (m, 2H), 1.91 (m, 2H), 1.49 (m, 2H), 1.21-1.02 (m, 9H), 0.86 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 160.8, 146.1, 137.6, 137.5, 130.0, 128.0, 127.9, 123.9, 122.8, 47.8, 39.2, 32.5, 31.8, 27.5, 27.1; FTIR (film) 2951.4, 2857.7, 1593.5,

1551.8, 1490.8, 1334.2  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 339.2 (26), 337.2 ( $\text{M}+\text{H}$ , 100), 336.2 (18); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 337.2280, found 337.2273.

*Benzoyl(2-methyl-6-neopentylpyridinium-1-yl)amide (3r)*. (56 mg, 66%);  $R_f$  = 0.3 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 40:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61-8.53 (m, 1H), 8.19 (m, 2H), 7.87-7.27 (m, 3H), 2.65 (s, 3H), 2.17 (s, 2H), 1.04 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.6, 153.7, 136.2, 130.0, 129.8, 128.0, 127.8, 126.6, 125.5, 123.2, 44.6, 30.0, 28.9, 20.5; FTIR (film) 3062.2, 2957.1, 2916.0, 2860.1, 1631.7, 1595.2, 1555.5, 1330.9  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 283.2 [ $\text{M}+\text{H}$ ]<sup>+</sup>, 100], 219.1 (5), 141.6(8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 283.1805, found 283.1805.

*Benzoyl(4-methyl-2-neopentylpyridinium-1-yl)amide (3s)*. (60 mg, 71%);  $R_f$  = 0.35 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.52 (d,  $J$  = 6.0 Hz, 1H), 8.18 (d,  $J$  = 5.2 Hz, 2H), 7.42-7.27 (m, 5H), 3.07 (s, 2H), 2.52 (s, 3H), 1.03 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.9, 153.9, 149.0, 145.3, 137.5, 129.9, 129.3, 128.0, 127.8, 124.2, 43.7, 33.8, 29.8, 21.3; FTIR (film) 3061.8, 2958.3, 2915.9, 2866.2, 1630.7, 1595.6, 1554.6, 1332.7  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 283.2 [ $\text{M}+\text{H}$ ]<sup>+</sup>, 100], 219.1 (5), 141.6 (8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{18}\text{H}_{23}\text{N}_2\text{O}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 283.1805, found 283.1805.

*Benzoyl(2-neopentyl-4-phenylpyridinium-1-yl)amide (3t)*. (80 mg, 78%);  $R_f$  = 0.3 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 30:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.81-8.72 (m, 1H), 8.22 (d,  $J$  = 4.0 Hz, 2H), 7.82 (m, 1H), 7.68 (m, 3H), 7.54 (m, 3H), 7.43(m, 3H), 3.09 (s, 2H), 1.08 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.8, 154.3, 148.5, 146.0, 135.6, 130.6, 129.9, 129.6, 128.1, 127.8, 127.3, 126.0, 123.2, 121.0, 44.1, 34.0, 29.9; FTIR (film) 2961.1, 2920.1, 1625.5, 1593.3, 1548.4, 1334.7  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 345.2 [ $\text{M}+\text{H}$ ]<sup>+</sup>, 100], 275.1 (8), 253.2 (8), 229.8 (7), 207.6 (5), 172.6 (8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 345.1961, found 345.1962.

*Benzoyl(2-neopentylquinolinium-1-yl)amide (3u)*. (67 mg, 70%);  $R_f$  = 0.3 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 20:1), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J$  = 8.8 Hz, 1H), 8.33 (m, 3H), 7.97 (d,  $J$  = 7.6 Hz,

1H), 7.81 (t,  $J = 7.4$  Hz, 1H), 7.69-7.60 (m, 2H), 7.47(m, 3H), 2.83 (s, 2H), 1.11 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  169.4, 157.6, 140.5, 137.4, 133.3, 130.0, 128.7, 128.5, 128.4, 128.2, 127.9, 124.5, 121.4, 46.0, 34.9, 30.3; FTIR (film) 3062.7, 2959.5, 2927.0, 2868.1, 1594.3, 1555.4, 1334.8  $\text{cm}^{-1}$ ; ESI-MS ( $m/z$ , relative intensity): 319.2  $[(\text{M}+\text{H})^+]$ , 100, 317.2 (60), 159.6 (8); HRMS (ESI)  $m/e$  calcd for  $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}$   $(\text{M}+\text{H})^+$  319.1805, found 319.1807.

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## Supporting Information

Deuterium exchange experiments, copies of  $^1\text{H}$  and  $^{13}\text{C}$  spectra for all products, details of DFT calculation. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

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