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

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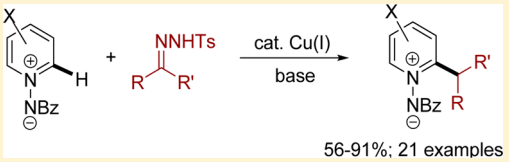
Supporting Information

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 uses inexpensive CuI as the catalyst without any ligand. The reaction is operationally simple and conducted under mild conditions, giving the corresponding alkylated pyridines in moderate to good yields. DFT calculation provides insights into the reaction mechanism, suggesting that the reaction proceeds through the Cu carbene migratory insertion process.

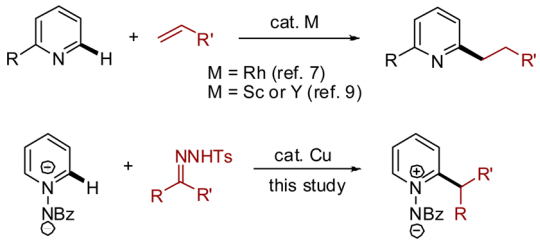


INTRODUCTION

The pyridine core is an important structural unit that exists widely in various natural products, pharmaceuticals, ligands, and synthetic building blocks.[1] The development of synthetic methodologies toward substituted pyridine derivatives, especially through direct C−H functionalization, has attracted great attention in recent years.[2−10] Early efforts in this area were focused on C2 lithiation of pyridines, followed by alkylation.[2a,c,4b] Another strategy involves the reaction of Grignard reagents with pyridine *N*-oxide as described by Almvist and Olsson.[4c] More recently, the transition-metal-catalyzed approach has become mainstream in these studies. In this context, Fagnou, Charette, Hiyama, and other groups have disclosed their pioneering work on transition-metal-catalyzed ortho-arylation or -alkenylation through C−H functionalization of pyridine *N*-oxides or *N*-iminopyridinium ylides.[5,6] This remarkable progress has made 2-aryl and 2-alkenyl pyridine derivatives easily available. In sharp contrast, the corresponding ortho-alkylation of pyridines with a similar strategy remains a challenging problem, largely due to the *β*-hydride elimination of transition metal alkyl species involved in the reaction pathway.

Recently, Bergman and Ellman have developed an approach toward ortho-alkylation of pyridines by using Rh(I)-phosphine complex-catalyzed C−H bond addition to olefins.[7,8] Moreover, Guan and Hou have reported that half-sandwich rare-earth dialkyl complexes and $B(C_6F_5)_3$ can serve as excellent catalyst systems for similar transformations (Scheme 1).[9,10] Although a significant breakthrough has been made for ortho-alkylation of pyridines, some drawbacks still remain. First, both reactions require expensive and/or complicated catalyst systems. Besides, the regioselectivity is a problem in the reaction with substituted olefins. Thus, the development of a more general method for highly selective ortho-alkylation of pyridines, ideally by using simple and inexpensive metal catalysts, is highly demanded.

Scheme 1. Transition-Metal-Catalyzed Ortho-Alkylation of Pyridines



We have recently reported a series of Cu-catalyzed cross-coupling reactions using *N*-tosylhydrazones as coupling partners.[11] These reactions presumably proceed through migratory insertion process of the Cu carbene intermediate.[12] As a continuation of our interest in this area, herein we report the first Cu-catalyzed direct alkylation of *N*-iminopyridinium ylides[6,13] 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).

RESULTS AND DISCUSSION

On the basis of the reports by Charette and co-workers,[6] 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 LiO*t*Bu in toluene,[14] 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

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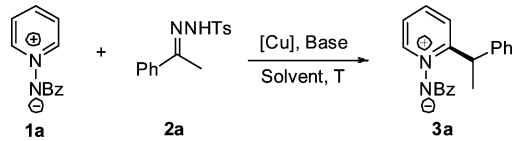
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	CuX (mol %)	base	solvent	T (°C)	yield (%)[b]
1	CuI (10)	LiO*t*Bu	dioxane	90	30
2	CuI (10)	LiO*t*Bu	DCE	90	34
3	CuI (10)	LiO*t*Bu	PhMe	90	66
4	CuI (10)	NaO*t*Bu	PhMe	90	22
5	CuI (10)	Cs_2CO_3	PhMe	90	31
6	CuI (10)	K_2CO_3	PhMe	90	24
7	CuI (10)	LiO*t*Bu	PhMe	110	53
8	CuI (10)	LiO*t*Bu	PhMe	80	23
9	CuBr (10)	LiO*t*Bu	PhMe	90	55
10	CuCl (10)	LiO*t*Bu	PhMe	90	45
11[c]	CuI (20)	LiO*t*Bu	PhMe	90	81

[a]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. [b]Isolated yield. [c]The reaction was carried out with 0.8 mmol *N*-tosylhydrazone and 1.4 mmol LiO*t*Bu.

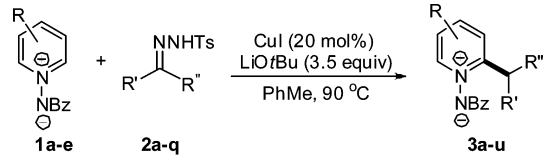
by screening the temperature and copper salts (Table 1, entries 7−10). We found that the initially used CuI provided better results as compared with other Cu salts. We then went on to screen other reaction parameters and observed that the reaction was significantly affected by the copper catalyst loading and the ratio of substrates. The optimal yield could be achieved by using 20 mol % of the CuI catalyst and LiO*t*Bu (3.5 equiv) in toluene, and the ratio of pyridinium ylide to *N*-tosylhydrazone is 1:2 (Table 1, entry 11).

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, alkoxyl, cyclopropyl, ester, and 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).

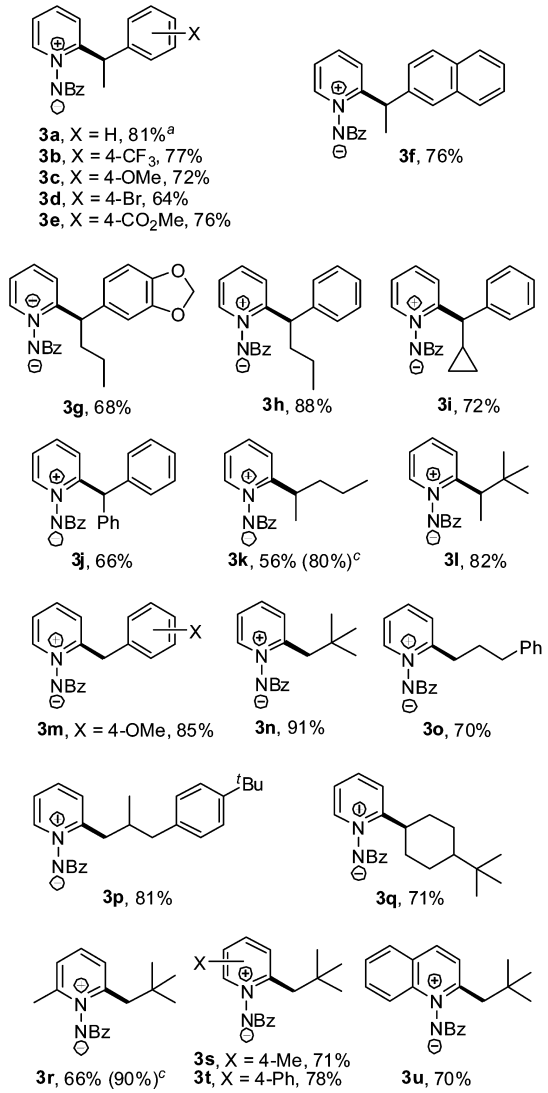
Next, the scope of *N*-iminopyridinium ylide was investigated. The reaction was examined with *N*-iminopyridinium ylides **1b−e**, which were treated with tosylhydrazones **2n** (R′ = H, R″ = *t*Bu) under the optimized reaction conditions. *N*-Iminopyridinium species with substituents at the 2- and 4-positions 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.

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.[6c,11] The key step in the reaction is proposed to be the migratory insertion of the Cu carbene species.

Scheme 2. Direct Alkylation of *N*-Iminopyridinium Ylides with *N*-Tosylhydrazones[a]



1a-e 2a-q 3a-u



[a]Reaction conditions if not otherwise noted: **1a−e** (0.3 mmol), **2a−q** (0.6 mmol), CuI (20 mol %), LiO*t*Bu (1.05 mmol), PhMe (2 mL), 5−8 h. [b]Isolated yield. [c]The yields in parentheses are these based on recovered starting materials.

In the presence of base and Cu(I) salt, the copper pyridinium ylide **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.

To have a better understanding of the reaction mechanism, density functional theory (DFT)[15] studies have been performed

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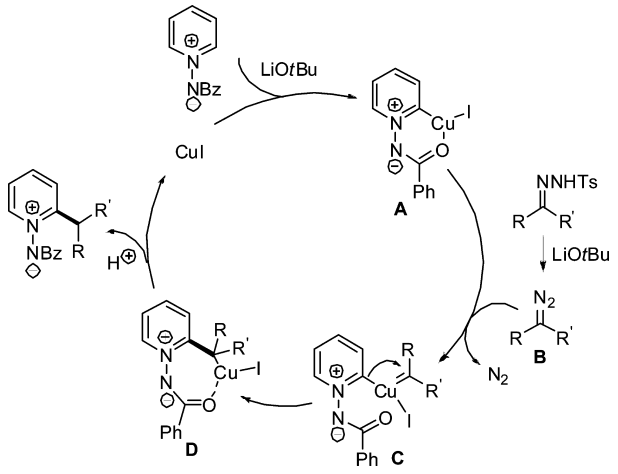
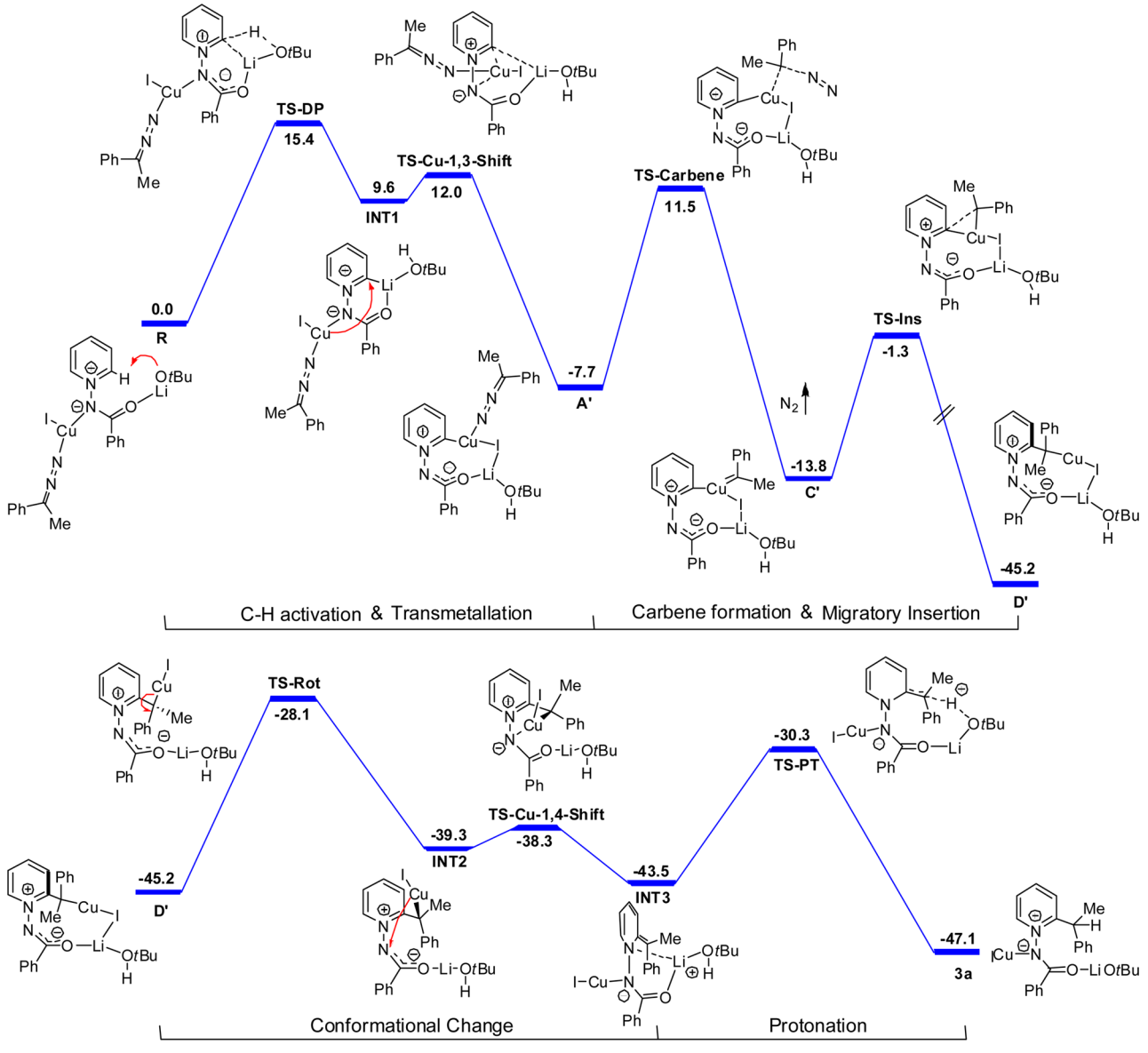
Scheme 3. Mechanistic Rationale



with the Gaussian 09 program[16] using the B3LYP[17] method. Based on an extensive computational study on many possible mechanisms, the whole reaction pathway was obtained.[18] For C, H, O, N, and Li, the 6-311+G** basis set was used. For Cu and I, the SDD[19] basis set with effective core potential (ECP) was used. The structures were optimized with the SMD[20] method in toluene (ε = 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

Scheme 4. The Calculated Full Reaction Pathway[a]



[a]The relative free energies in solvent ΔG_{sol} are in kcal/mol, calculated at B3LYP/6-311+G**/SDD level.

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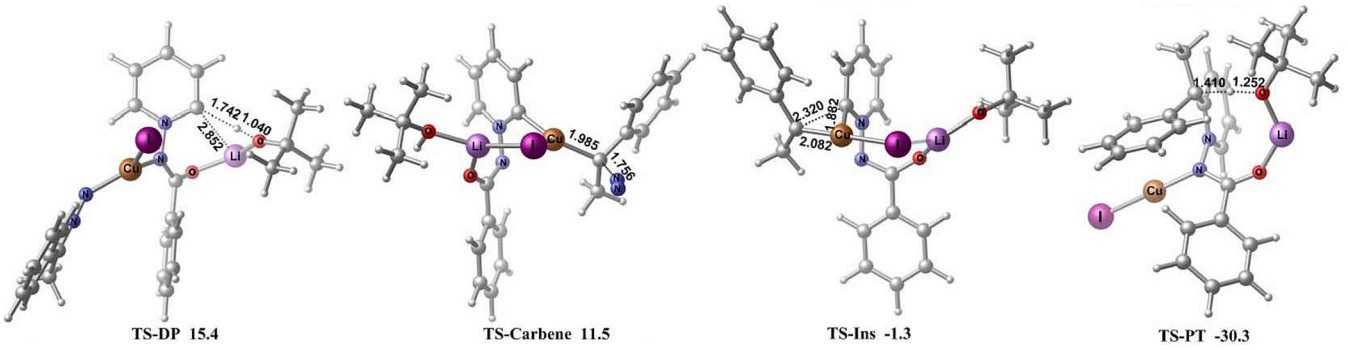
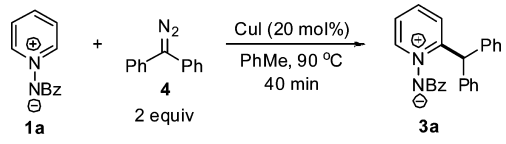


Figure 1. The optimized important transition states on the full reaction pathways. Bond lengths are in angstroms (Å), and relative free energies in solvent ΔG_{sol} are in kcal/mol, calculated at the B3LYP/6-311+G**/SDD level.

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 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.[18] The key transition states along the reaction coordinate are shown in Figure 1.

The results of the 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 the C−H bond of heterocycles cannot be strictly eliminated.[21] To verify such a possible pathway, a control experiment has been carried out. Thus, diphenyldiazomethane **4** was prepared and was subjected to CuI-catalyzed reaction with *N*-iminopyridinium ylide **1a** (Scheme 5). In the absence of base, only trace product

Scheme 5. Control Experiments with Diphenyldiazomethane 4

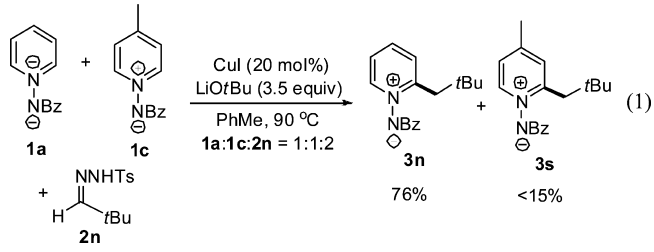


Base	Yield
none	trace
LiO*t*Bu (1.5 equiv)	58%

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 the Cu carbene C−H insertion mechanism can be ruled out because of the unfavorable energy barrier.[18]

Charette and co-workers have carried out deuterium exchange experiments in their Cu-catalyzed ortho-alkenylation of *N*-iminopyridinium ylides.[6c] The study indicates that deprotonation occurs at the 2,6-positions of the pyridinium ring in the presence of $CuBr_2$ (10 mol %) and K_2CO_3 (2 equiv). Our deuterium exchange experiments also suggest preferential deprotonation at 2,6-positions in the presence of CuI (20 mol %) and LiO*t*Bu (3.5 equiv). Furthermore, DFT calculation shows that protons at 2,6-positions of pyridinium ring are more acidic than those at 3,4-positions.[18]

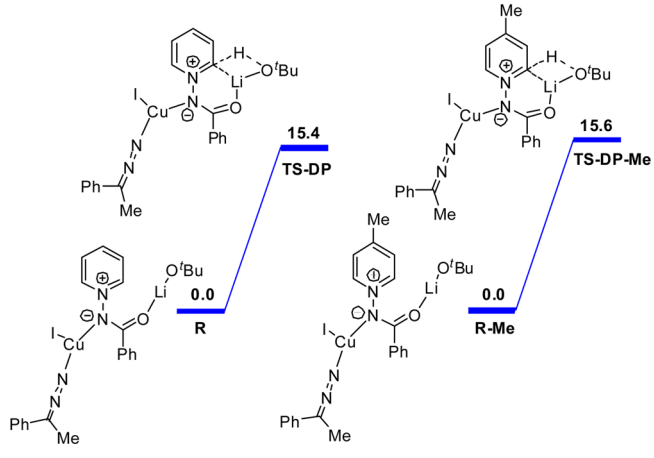
To gain further insights, the effect of substituents on the reaction was studied (eq 1). The competition experiment of



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 ΔG_{sol} (1.0 kcal/mol in ΔE_{sol}) higher than that of **1a**, which qualitatively agrees

Scheme 6. Calculation on Substituent Effects[a]



[a]The relative free energies in solvent ΔG_{sol} are in kcal/mol, calculated at B3LYP/6-311+G**/SDD level.

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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.

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 inexpensive 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. Because *N*-tosylhydrazones are easily prepared from the corresponding aldehydes or ketones, this reaction represents a practical access toward various 2-alkylpyridines. 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_2. Silica gel (200−300 mesh) was used for the chromatography. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in ppm using tetramethylsilane (TMS) as the internal standard. IR spectra are reported in wave numbers, cm^{-1}. For HRMS measurements, the mass analyzer is FT-ICR.

The Preparation of *N*-Tosylhydrazones (2a−q). The literature procedure was followed.[11] A solution of pure $TsNHNH_2$ (5 mmol) in methanol (5 mL) was stirred and heated to 60 °C until the $TsNHNH_2$ dissolved. The mixture was cooled to room temperature. Then carbonyl compounds were dropped into the mixture slowly. After approximately 5 min, the crude products could be obtained as solid precipitates. The precipitates were washed with 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). The literature procedure was followed.[6] Pyridine (0.100 mL, 1.24 mmol) and *O*-(2,4-dinitrophenyl)hydroxylamine (272 mg, 1.36 mmol) were added to H_2O/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 and 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_2O (5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were washed with NaOH (2.5 N, 5 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording the *N*-iminopyridinium ylides **1a−e**. The ^{1}H NMR spectra data of **1a−e** were found consistent with those previously reported in the literature.[6]

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) and LiO*t*Bu (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_2Cl_2/MeOH = 40:1) to afford pure **3a** as a yellow oil (73 mg, 81%).

Benzoyl(2-(1-phenylethyl)pyridinium-1-yl)amide (3a):[6b] 73 mg, 81%; R_f = 0.3 (CH_2Cl_2:MeOH = 40:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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):[6b] 85 mg, 77%; R_f = 0.4 (CH_2Cl_2:MeOH = 30:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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):[6b] 72 mg, 72%; R_f = 0.35 (CH_2Cl_2:MeOH = 40:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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}C NMR (100 MHz, $CDCl_3$) δ 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 (CH_2Cl_2:MeOH = 40:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 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 $C_{20}H_{18}BrN_2O$ (M + H)$^+$ 381.0597, found 381.0603.

Benzoyl(2-(1-(4-(methoxycarbonyl)phenyl)ethyl)pyridinium-1-yl)amide (3e):[6b] 82 mg, 76%; R_f = 0.3 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 (CH_2Cl_2:MeOH = 30:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 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 $C_{24}H_{21}N_2O$ (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_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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^{-1}; ESI-MS (m/z, relative intensity): 375.2 [(M + H)$^+$, 100], 310.7 (3), 167.6 (8), 177.1 (5); HRMS (ESI) m/e calcd for $C_{23}H_{23}N_2O_3$ (M + H)$^+$ 375.1703, found 375.1709.

Benzoyl(2-(1-phenylbutyl)pyridinium-1-yl)amide (3h): 87 mg, 88%; R_f = 0.3 (CH_2Cl_2:MeOH = 40:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.2 Hz, 1H), 8.14 (d, J = 3.2 Hz, 2H),

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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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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^{-1}; ESI-MS (m/z, relative intensity): 331.2 [(M + H)$^+$, 100], 176.6 (5), 165.6 (3); HRMS (ESI) m/e calcd for $C_{22}H_{23}N_2O$ (M + H)$^+$ 331.1805, found 331.1805.

Benzoyl(2-(cyclopropyl(phenyl)methyl)pyridinium-1-yl)-amide (3i): 71 mg, 72%; R_f = 0.3 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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^{-1}; ESI-MS (m/z, relative intensity): 329.2 [(M + H)$^+$, 100], 165.6 (3); HRMS (ESI) m/e calcd for $C_{22}H_{21}N_2O$ (M + H)$^+$ 329.1654, found 329.1655.

(2-Benzhydrylpyridinium-1-yl)(benzoyl)amide (3j):[6b] 72 mg, 66%; R_f = 0.35 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (300 MHz, $CDCl_3$,) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 (CH_2Cl_2:MeOH = 30:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 269.2 [(M + H)$^+$, 100], 221.2 (15), 134.6 (7), 105.0 (5); HRMS (ESI) m/e calcd for $C_{17}H_{21}N_2O$ (M + 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 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 283.2 [(M + H)$^+$, 100), 195.8 (8), 141.6 (5), 99.3 (3); HRMS (ESI) m/e calcd for $C_{18}H_{23}N_2O$ (M + H)$^+$ 283.1805, found 283.1806.

Benzoyl(2-(4-methoxybenzyl)pyridinium-1-yl)amide (3m):[6b] 81 mg, 85%; R_f = 0.4 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 (CH_2Cl_2:MeOH = 20:1), brown oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 269.2 [(M + H)$^+$, 100], 169.6 (8); HRMS (ESI) m/e calcd for $C_{17}H_{21}N_2O$ (M + H)$^+$ 269.1648, found 269.1652.

Benzoyl(2-(3-phenylpropyl)pyridinium-1-yl)amide (3o): 66 mg, 70%; R_f = 0.3 (CH_2Cl_2:MeOH = 30:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 317.2 [(M + H)$^+$, 100], 158.6 (8); HRMS (ESI) m/e calcd for $C_{21}H_{21}N_2O$ (M + 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 (CH_2Cl_2:MeOH = 40:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 387.2 [(M + H)$^+$, 100], 193.6 (5), 141.6 (8); HRMS (ESI) m/e calcd for $C_{26}H_{31}N_2O$ (M + H)$^+$ 387.2431, found 387.2434.

Benzoyl(2-(4-*tert*-butylcyclohexyl)pyridinium-1-yl)amide (3q): 71 mg, 71%; R_f = 0.3 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 339.2 (26), 337.2 (M + H, 100), 336.2 (18); HRMS (ESI) m/e calcd for $C_{22}H_{29}N_2O$ (M + H)$^+$ 337.2280, found 337.2273.

Benzoyl(2-methyl-6-neopentylpyridinium-1-yl)amide (3r): 56 mg, 66%; R_f = 0.3 (CH_2Cl_2:MeOH = 40:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 283.2 [(M + H)$^+$, 100], 219.1 (5), 141.6(8); HRMS (ESI) m/e calcd for $C_{18}H_{23}N_2O$ (M + H)$^+$ 283.1805, found 283.1805.

Benzoyl(4-methyl-2-neopentylpyridinium-1-yl)amide (3s): 60 mg, 71%; R_f = 0.35 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 283.2 [(M + H)$^+$, 100], 219.1 (5), 141.6 (8); HRMS (ESI) m/e calcd for $C_{18}H_{23}N_2O$ (M + H)$^+$ 283.1805, found 283.1805.

Benzoyl(2-neopentyl-4-phenylpyridinium-1-yl)amide (3t): 80 mg, 78%; R_f = 0.3 (CH_2Cl_2:MeOH = 30:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 345.2 [(M + H)$^+$, 100], 275.1 (8), 253.2 (8), 229.8 (7), 207.6 (5), 172.6 (8); HRMS (ESI) m/e calcd for $C_{23}H_{25}N_2O$ (M + H)$^+$ 345.1961, found 345.1962.

Benzoyl(2-neopentylquinolinium-1-yl)amide (3u): 67 mg, 70%; R_f = 0.3 (CH_2Cl_2:MeOH = 20:1), brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 cm^{-1}; ESI-MS (m/z, relative intensity): 319.2 [(M + H)$^+$, 100], 317.2 (60), 159.6 (8); HRMS (ESI) m/e calcd for $C_{21}H_{23}N_2O$ (M + H)$^+$ 319.1805, found 319.1807.

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■ ASSOCIATED CONTENT

Supporting Information

Deuterium exchange experiments, copies of ^{1}H and ^{13}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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Notes

The authors declare no competing financial interest.

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