

# Palladium-Catalyzed Oxidative Acetoxylation of Benzylic C–H Bond Using Bidentate Auxiliary

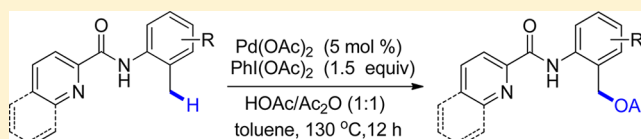
Long Ju,<sup>†</sup> Jinzhong Yao,<sup>†</sup> Zaihong Wu,<sup>†</sup> Zhanxiang Liu,<sup>\*,†</sup> and Yuhong Zhang<sup>\*,†,‡</sup>

<sup>†</sup>ZJU-NHU United R&D Center, Department of Chemistry, Zhejiang University, Hangzhou 310027, China

<sup>‡</sup>State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

**S** Supporting Information

**ABSTRACT:** Pd(OAc)<sub>2</sub>-catalyzed oxidative acetoxylation of benzylic C–H bonds utilizing a bidentate system has been explored. A variety of picolinoyl- or quinoline-2-carbonyl-protected toluidine derivatives react with PhI(OAc)<sub>2</sub> in the presence of Pd(OAc)<sub>2</sub> to afford the acetoxyated products in synthetically useful yields. A broad of functionalities, such as CH<sub>3</sub>, F, Cl, Br, I, COCH<sub>3</sub>, CO<sub>2</sub>Et, SO<sub>2</sub>CH<sub>3</sub>, and NO<sub>2</sub>, were tolerated. This transformation provides easy access to 2-hydroxymethylaniline derivatives.



## INTRODUCTION

Transition-metal-catalyzed C–H activation reactions provide a powerful tool for step-economical syntheses of the pharmaceutical targets, bioactive molecules, and materials.<sup>1</sup> Among these reactions, oxidative C–H bond acetoxylation is one of the most straightforward strategies for the formation of C–O bonds.<sup>2,3</sup> Over the past decades, Pd-catalyzed ligand-directed C–H oxidation has emerged as a powerful approach to achieve C(sp<sup>3</sup>)–H acetoxylation.<sup>4</sup> Various directing groups, such as pyridine,<sup>5a,b</sup> quinoline,<sup>5c</sup> O-methyl oxime,<sup>5d–f</sup> oxazoline,<sup>6a</sup> amides,<sup>6b</sup> and the oxime,<sup>7</sup> have been successfully employed for Pd-catalyzed C(sp<sup>3</sup>)–H acetoxylation by the research groups of Sanford, Yu, and others. In addition to these monodentate directing groups, the bidentate auxiliaries provide a new alternative way for functionalization of C(sp<sup>3</sup>)–H bonds due to their superior directing abilities.<sup>8</sup> In this regard, Corey has described the pioneering examples of β-acetoxylation of C(sp<sup>3</sup>)–H bonds in amino acid derivatives by employing the 8-aminoquinoline auxiliary.<sup>9</sup> More recently, Chen has reported an elegant work on the Pd-catalyzed, picolinamide (PA)-directed alkoxylation of unactivated C(sp<sup>3</sup>)–H bonds at remote positions using alcohols.<sup>8g</sup> Sahoo and co-workers demonstrated an approach of β-C(sp<sup>3</sup>)–H acetoxylation by using S-methyl-S-2-pyridylsulfoximine (MpyS) as a bidentate directing group.<sup>10</sup>

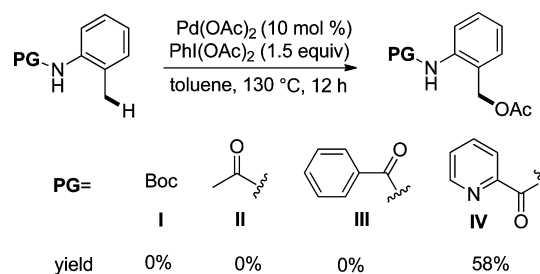
The benzyl group is an important motif of organic synthesis and serves as a valuable synthetic intermediate in various transformations. Catalytic acetoxylation processes for the functionalization of the benzylic C(sp<sup>3</sup>)–H bonds are of great synthetic interest. Our group has reported that a picolinamide moiety can be used as the chelating group for arylation/oxidation of benzylic C–H bonds.<sup>11</sup> Based on the previous work, we expected that the bidentate system could serve as a good directing group for the acetoxylation of benzylic C–H bonds. Herein, we report Pd(OAc)<sub>2</sub> catalyzed oxidative acetoxylation of the benzylic C–H bond of picolinoyl-protected

toluidines using PhI(OAc)<sub>2</sub> as an oxidant and the acetate source.

## RESULTS AND DISCUSSION

In recent years, amide has been widely utilized as potential directing group in the metal-catalyzed C–H activation.<sup>12</sup> In our initial research, we employed acetamide, benzamide, and Boc-carbamate as directing groups for the acetoxylation benzylic C–H bond in the presence of PhI(OAc)<sub>2</sub>/Pd(OAc)<sub>2</sub>, which has been shown to be a privileged system in C–H bond acetoxylation. The reaction was performed in toluene at 130 °C (Scheme 1). Unfortunately, we found that all of these

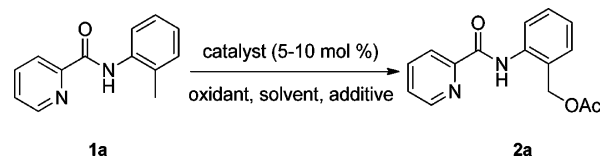
**Scheme 1. Effect of Directing Group**



monodentate directing groups are totally unreactive (Scheme 1, I–III). In light of the remarkable success of bidentate systems, we explored the picolinoyl-protected toluidine as substrate under otherwise identical reaction conditions: Pd(OAc)<sub>2</sub> (10 mol %), PhI(OAc)<sub>2</sub> (1.5 equiv), in 2 mL toluene at 130 °C for 12 h. To our delight, the expected benzylic C–H acetoxylation product was achieved in 58% yield (Scheme 1, IV). This result

Received: August 19, 2013

Published: October 9, 2013

Table 1. Pd-Catalyzed PA-Directed Acetoxylation of Benzylic C–H Bonds: Variation of Reaction Conditions<sup>a</sup>

entry	catalyst (mol %)	oxidant (equiv)	additive	solvent	temp (°C)	yield (%)
1	Pd(OAc) <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)		PhMe	130	58
2	Pd(OAc) <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	60
3	Pd(OAc) <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (10:1)	PhMe	130	51
4	Pd(OAc) <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	79
5	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	65
6	Pd(PPh <sub>3</sub> ) <sub>4</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	68
7	PdCl <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	42
8	Pd(MeCN) <sub>2</sub> Cl <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	65
9	Pd(dba) <sub>2</sub> (10)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	68
10	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	79
11	Pd(OAc) <sub>2</sub> (5)	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	trace
12	Pd(OAc) <sub>2</sub> (5)	Oxone (1.5)	HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	n.r.
13	Pd(OAc) <sub>2</sub> (5)	Cu(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	n.r.
14	Pd(OAc) <sub>2</sub> (5)	AgOAc (1.5)	HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	n.r.
15	Pd(OAc) <sub>2</sub> (5)		HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	n.r.
16		PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:10)	PhMe	130	n.r.
17	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.0)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	54
18	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (2.0)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	72
19	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (3.0)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	68
20	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	DMF	130	trace
21	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	DMSO	130	trace
22	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	<i>t</i> -AmylOH	130	trace
23	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	xylene	130	63
24	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	61 <sup>b</sup>
25	Pd(OAc) <sub>2</sub> (5)	PhI(OAc) <sub>2</sub> (1.5)	HOAc/Ac <sub>2</sub> O (1:1)	PhMe	130	65 <sup>c</sup>

<sup>a</sup>Reaction conditions: **1a** (0.3 mmol), Pd catalyst (5–10 mol %), solvent (2 mL), 20 min at rt, heating to 130 °C for 12 h. <sup>b</sup>Under argon atmosphere. <sup>c</sup>Under O<sub>2</sub> atmosphere.

indicates that coordination in an *N*, *N'*-fashion by the picolinamide is essential for the reaction to proceed.

Encouraged by the promising result, we attempted to optimize the reaction conditions. We found that addition of Ac<sub>2</sub>O and HOAc can promote the Pd(OAc)<sub>2</sub>-catalyzed C–H acetoxylation. For instance, we examined the reaction of picolinoyl-protected toluidine **1a** in the presence of Pd(OAc)<sub>2</sub> and PhI(OAc)<sub>2</sub> in the mixed solvents of acetic anhydride and acetic acid (1:1, 1 equiv) in toluene (2 mL) at 130 °C. Gratifyingly, the yield of benzylic C–H acetoxylation product **2a** was increasingly improved from 58% to 79% (Table 1, entries 2–4). These conditions have been shown to affect Pd-catalyzed directed arene acetoxylation reported by Sanford.<sup>13</sup>

Other palladium catalysts were tested in the model reaction. When Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, PdCl<sub>2</sub>, Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Pd(dba)<sub>2</sub> were employed as catalyst precursors in the presence of PhI(OAc)<sub>2</sub>, the reaction gave slightly reduced yields (Table 1, entries 5–9). It is evident that Pd(OAc)<sub>2</sub> was the most effective catalyst for this transformation. Interestingly, lowering the Pd(OAc)<sub>2</sub> catalyst loading from 10 to 5 mol % has no significant effect on product yield. The reaction using 5 mol % of Pd(OAc)<sub>2</sub> could also afford a 79% yield (Table 1, entry 10).

We have also investigated various alternative oxidants. K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, oxone, copper acetate, and silver acetate completely failed to promote any useful transformations (Table 1, entries 11–14). PhI(OAc)<sub>2</sub> clearly stood out and afforded the best results. Furthermore, control experiments confirmed that the

palladium catalyst and PhI(OAc)<sub>2</sub> were necessary in this process. No desired product was observed in the absence of PhI(OAc)<sub>2</sub> or palladium catalysts (Table 1, entries 15 and 16). We envisioned that PhI(OAc)<sub>2</sub> might be playing other roles than just a simple oxidant, it might also serve as an acetate source. With respect to the oxidant loading, 1.5 equiv of PhI(OAc)<sub>2</sub> was found to be optimal (Table 1, entries 17–19).

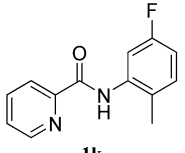
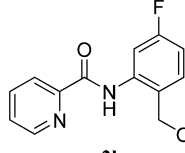
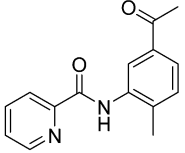
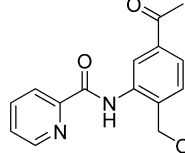
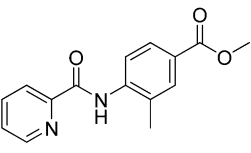
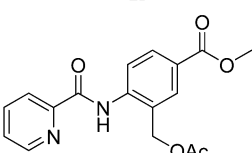
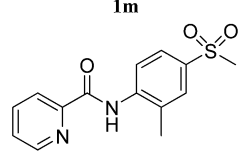
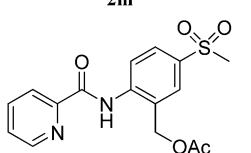
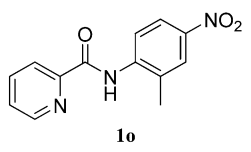
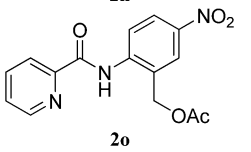
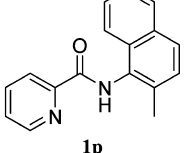
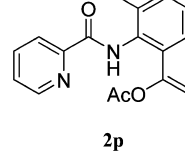
Among the solvents examined, DMF, DMSO, and *tert*-amyl-OH failed to facilitate this reaction (Table 1, entries 20–22). Xylene merely afforded 63% yield (Table 1, entry 23). Toluene was found to be the best solvent. In addition, the oxidative acetoxylation reaction performed slightly better under an air atmosphere than Ar (Table 1, entry 24) and O<sub>2</sub> atmosphere (Table 1, entry 25). As a result, when the reaction was carried out in the presence of 5 mol % of Pd(OAc)<sub>2</sub> with 1.5 equiv of PhI(OAc)<sub>2</sub> as the oxidant and 1.0 equiv of AcOH/Ac<sub>2</sub>O (1:1) in toluene as the cosolvent at 130 °C under air for 12 h, the best result was achieved.

With the optimized conditions in hand, we examined the scope of the Pd-catalyzed acetoxylation of benzylic C–H bonds with a diverse array of substituted toluidines (Table 2). The electron-donating and electron-withdrawing substituents in the aryl ring of toluidines were well tolerated to give moderate or high yields (Table 2, entries 2–16). A variety of functional groups, including methyl, fluoride, chloride, bromide, iodide, ester, and nitro substituents, were compatible with the reaction conditions. For example, arenes with a methyl group at the

Table 2. Pd-Catalyzed PA-Directed Acetoxylation of Benzylic C–H Bonds<sup>a</sup>

entry	substrate <b>1</b>	product	yield (%)
1			79
2			73
3			68
4			74
5			trace
6			75
7			71
8			72
9			76
10			49

Table 2. continued

entry	substrate <b>1</b>	product	yield (%)
11	 <b>1k</b>	 <b>2k</b>	79
12	 <b>1l</b>	 <b>2l</b>	62
13	 <b>1m</b>	 <b>2m</b>	65
14	 <b>1n</b>	 <b>2n</b>	59
15	 <b>1o</b>	 <b>2o</b>	49
16	 <b>1p</b>	 <b>2p</b>	54

<sup>a</sup>Reaction conditions: **1a** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.015 mmol, 6 mg), PhI(OAc)<sub>2</sub> (0.45 mmol, 145 mg), 1.0 equiv of AcOH/Ac<sub>2</sub>O (1:1), toluene (2 mL), under air, 12 h, 130 °C.

*meta* and *para* positions afforded the products in good yields (Table 2, entries 2–4). Arenes with an *ortho* substituent delivered the corresponding product in lower yield (Table 2, entry 5), illustrating that the steric hindrance played the role to the reaction.<sup>8f</sup> Picolinoyl-protected toluidine with phenyl group at *para* position achieved 75% yield (Table 2, entry 6). It should be noted that iodo, bromo, and chloro groups were tolerated, which provides the possibility for further modification of the molecules (Table 2, entries 7–9). Arenes bearing a fluoro group at the *para* position (Table 2, entry 10) afforded a relatively lower yield than its analogues (Table 2, entry 11). Importantly, arenes with strong electron-withdrawing groups, such as ketone, ester, sulfone, and nitro groups, participated in the reaction smoothly to give the acetoxylation products in good yields (Table 2, entries 12–15). It was interesting that the functionalization of C(sp<sup>2</sup>)-H occurred preferably to give the corresponding product **2p** when the substrate **1p** was used (Table 2, entry 16). The reaction of arenes with hydroxy<sup>3c</sup> and carboxyl groups failed to give the acetoxylation products under the reaction conditions due to the strong coordination of these functionalities with palladium.

It was well known that quinoline was an important motif of pharmaceuticals.<sup>14</sup> We envisioned that a similar approach might be applied to the acetoxylation of quinoline-2-carbonyl-protected toluidine substrates. In fact, the quinoline-2-carbonyl-protected toluidine with either electron-donating or electron-withdrawing groups could be utilized to afford the desired products **4b–j** in good yields (Table 3). For instance, substituted toluidines with a methyl group at the *meta*- or *para*-position of the phenyl ring gave comparable product yields of 64–67% (Table 3, entries 2–4). Quinoline-2-carbonyl-protected toluidines with a weak electron-withdrawing group such as iodo, bromo, chloro, fluoro, ester group at the *para*- or *meta*-position of the phenyl ring also afforded a corresponding product in good yields (Table 3, entries 5–10). Compared to the picolinoyl-protected toluidines, the reaction of the quinoline-2-carbonyl-protected toluidine substrates does not show any profound electronic preference.

Previous research demonstrated that the C–H acetoxylation might occur via an oxidative radical mechanism by the use of PhI(OAc)<sub>2</sub>.<sup>15</sup> In order to gain more information for the reaction mechanism, we performed the control experiments by adding the radical scavenger TEMPO under the standard

Table 3. Pd-Catalyzed Quinoline-2-carboxamide Directed Acetoxylation of Benzylic C–H Bonds<sup>a</sup>

entry	substrate	product	yield (%)
1			65
2			67
3			65
4			64
5			67
6			73
7			64
8			61

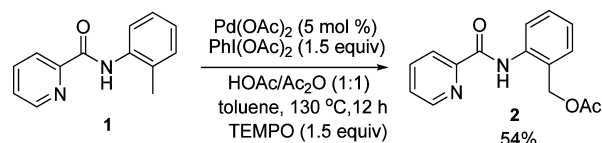
Table 3. continued

entry	substrate	product	yield (%)
9			68
10			57

<sup>a</sup>Reaction conditions: **3** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.015 mmol, 6 mg), PhI(OAc)<sub>2</sub> (0.45 mmol, 145 mg), 1.0 equiv of AcOH/Ac<sub>2</sub>O (1:1), toluene (2 mL), under air, 12 h, 130 °C.

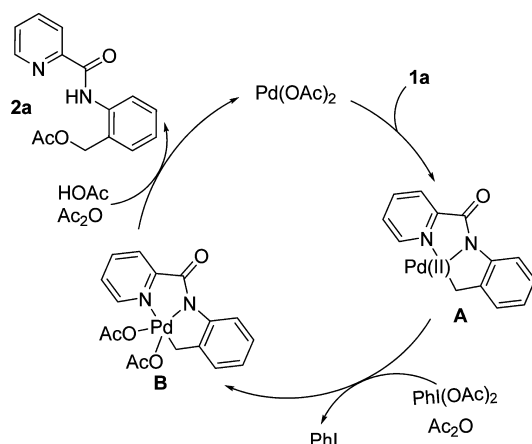
reaction conditions. It was found that the acetoxylation product **2** was still obtained in 54% (Scheme 2). This result suggested that the free-radical intermediate might not be involved in the reaction.

#### Scheme 2. Acetoxylation of Benzylic C–H in the Presence of TEMPO



Although details about the mechanism remain to be ascertained, based on the known chemistry of bidentate assisted C(sp<sup>3</sup>)–H activation,<sup>8,9</sup> a plausible mechanism of the palladium-catalyzed acetoxylation of benzylic C–H bonds with a series of anilines substrates was depicted in Scheme 3. The

#### Scheme 3. Plausible Mechanism

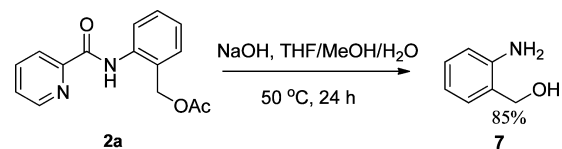


reaction might proceed via a Pd<sup>II</sup>/Pd<sup>IV</sup> pathway.<sup>3a,c,5d,6a</sup> The coordination of the substrate **1a** with Pd(OAc)<sub>2</sub> led to the formation of a palladacycle intermediate **A** by directed C–H activation. The palladacycle intermediate **A** is oxidized by PhI(OAc)<sub>2</sub> in the presence of Ac<sub>2</sub>O and HOAc to afford a Pd(IV) center intermediate **B**, which undergoes a reductive elimination process to furnish the acetoxylation products and

liberates the Pd(II) catalyst.<sup>16</sup> In this transformation, the absence of Ac<sub>2</sub>O results in the decreasing of the yields. Although there is no solid evidence for the role of Ac<sub>2</sub>O, the investigations demonstrate that the presence of Ac<sub>2</sub>O might lead to the accelerating of the formation of intermediate **B**.<sup>8f,9,13</sup>

Further experiments showed that the directing group can be removed under base hydrolysis affording 2-aminobenzyl alcohol derivative (Scheme 4).<sup>8f</sup> 2-(Picolinamido)benzyl acetate **2a** was

#### Scheme 4. Hydrolysis of Amide **2**



successfully hydrolyzed by NaOH in THF/MeOH/H<sub>2</sub>O to afford the product **7** in 85% yield. 2-Aminobenzyl alcohol is a useful synthetic intermediate for the synthesis of heterocyclic compound such as 4*H*-benzo[*d*][1,3]oxazine and quinoline.<sup>17</sup>

## CONCLUSION

In conclusion, we have developed a new protocol for Pd-catalyzed oxidative acetoxylation of the benzylic C–H bond by employing a bidentate system. Both picolinamide and quinoline-2-carboxamide could behave as the efficient controlling auxiliary. This new transformation tolerates certain functional groups. The amide auxiliary is effectively removed under mild conditions to provide a new synthetic method for 2-amino benzyl alcohol derivatives. Further exploration of the substrate scope and synthetic utility of this bidentate system are in progress in our laboratory.

## EXPERIMENTAL SECTION

General functionalized picolinamide derivatives **1a–k,m,o,p** and **3a–j** were prepared according to the literature.<sup>18</sup> In addition, the synthetic methods of **1l** and **1n** are described in the corresponding paragraphs. The other materials and solvents were purchased from common commercial sources and used without additional purification. NMR spectra were recorded for <sup>1</sup>H NMR at 400 or 500 MHz and <sup>13</sup>C NMR at 100 or 125 MHz using TMS as internal standard. The following abbreviations are used to describe peak patterns where appropriate: singlet (s), doublet (d), triplet (t), multiplet (m), broad resonances (br). Mass spectroscopy data of the products was collected on an

HRMS-EI-TOF. Infrared spectra were recorded on a FTIR spectrometer.

**General Procedure for Preparation of Functionalized Picolinamide Derivatives.** Aniline derivatives (20 mmol), picolinic acid (24 mmol), and Et<sub>3</sub>N (6 mL) were dissolved in dichloromethane (30 mL) followed by dropwise addition of POCl<sub>3</sub> (4 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. Then 50 mL water was added slowly to quench the reaction. The organic layer was collected and dried over MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give the desired product.

**Characterization Data of the Picolinamide Derivatives.** *N*-Tolylpicolinamide<sup>18</sup> (**1a**): white solid (3.45 g, 81% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.09 (s, 1H), 8.61 (dd, *J* = 4.4 Hz, 0.4 Hz, 1H), 8.31–8.28 (m, 2H), 7.89 (dt, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.48–7.44 (m, 1H), 7.29–7.25 (m, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.10–7.06 (m, 1H), 2.41 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.8, 150.0, 148.0, 137.6, 135.8, 130.3, 127.9, 126.8, 126.3, 124.5, 122.3, 121.2, 17.6.

*N*-(2,5-Dimethylphenyl)picolinamide<sup>18</sup> (**1b**): white solid (3.51 g, 78% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.04 (s, 1H), 8.61 (m, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 7.92–7.88 (m, 1H), 7.49–7.45 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 2.37 (s, 6H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.7, 150.1, 148.0, 137.5, 136.5, 135.6, 130.1, 126.3, 125.2, 124.8, 122.2, 121.8, 21.2, 17.2.

*N*-(2,4-Dimethylphenyl)picolinamide<sup>18</sup> (**1c**): white solid (3.78 g, 84% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 9.99 (s, 1H), 8.59 (d, *J* = 4.0 Hz, 1H), 8.28 (d, *J* = 7.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.87 (dt, *J* = 8.0 Hz, 2.4 Hz, 1H), 7.46–7.42 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 2.36 (s, 3H), 2.31 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.7, 150.1, 148.0, 137.5, 134.0, 133.2, 131.0, 128.1, 127.3, 126.2, 122.2, 121.3, 20.8, 17.6.

*N*-(2,3-Dimethylphenyl)picolinamide<sup>18</sup> (**1d**): white solid (3.62 g, 80% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.05 (s, 1H), 8.61 (m, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.89 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.48–7.45 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.9, 150.1, 148.0, 137.5, 137.1, 135.5, 127.6, 126.6, 126.3, 125.9, 122.3, 120.1, 20.6, 13.5.

*N*-(2,6-Dimethylphenyl)picolinamide<sup>19</sup> (**1e**): white solid (3.51 g, 78% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 9.48 (s, 1H), 8.63 (d, *J* = 4.8 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.90 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.50–7.47 (m, 1H), 7.14–7.10 (m, 3H), 2.30 (s, 6H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 162.3, 149.9, 148.2, 137.6, 135.4, 133.8, 128.2, 127.2, 126.4, 122.6, 121.0, 18.6.

*N*-(3-Methylbiphenyl-4-yl)picolinamide (**1f**): white solid (4.3 g, 74% yield); mp 108–110 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.16 (s, 1H), 8.62 (d, *J* = 4.4 Hz, 1H), 8.38 (d, *J* = 4.4 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.91 (dt, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.53–7.41 (m, 5H), 7.34–7.31 (m, 1H), 2.50 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.9, 150.1, 148.1, 140.8, 137.8, 137.4, 135.3, 129.1, 128.8, 128.3, 127.1, 126.9, 126.5, 125.6, 122.5, 121.5, 17.9; HRMS (EI) calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O (M<sup>+</sup>) 288.1263, found 288.1264; IR (neat, cm<sup>-1</sup>) ν 3333, 3026, 2983, 1681, 1530, 1429, 999, 763, 685.

*N*-(4-Iodo-2-methylphenyl)picolinamide<sup>11</sup> (**1g**): white solid (4.87 g, 84% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.07 (s, 1H), 8.61 (d, *J* = 4.8 Hz, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.90 (dt, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.57–7.55 (m, 2H), 7.50–7.46 (m, 1H), 2.36 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.8, 149.7, 148.0, 138.8, 137.6, 135.7, 129.9, 126.5, 122.6, 122.3, 87.9, 17.2.

*N*-(4-Bromo-2-methylphenyl)picolinamide<sup>18</sup> (**1h**): white solid (4.94 g, 85% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.07 (s, 1H), 8.61–8.60 (m, 1H), 8.27 (d, *J* = 7.2 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.90 (dt, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.50–7.46 (m, 1H), 7.38–7.35 (m, 2H), 2.38 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.7, 149.7, 148.0, 137.6, 134.9, 132.9, 129.9, 129.7, 126.5, 122.4, 122.3, 117.0, 17.4.

*N*-(4-Chloro-2-methylphenyl)picolinamide<sup>18</sup> (**1i**): white solid (3.82 g, 78% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.07 (s, 1H), 8.62 (d, *J* = 4.0 Hz, 1H), 8.29–8.24 (m, 2H), 7.91 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.49–7.48 (m, 1H), 7.24–7.20 (m, 2H), 2.40 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.8, 149.7, 148.0, 137.6, 134.4, 130.1, 129.6, 129.2, 126.7, 126.5, 122.3, 122.2, 17.5.

*N*-(4-Fluoro-2-methylphenyl)picolinamide<sup>18</sup> (**1j**): white solid (3.24 g, 71% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 9.97 (s, 1H), 8.61 (dd, *J* = 4.8 Hz, 0.8 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.16–8.13 (m, 1H), 7.90 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.49–7.46 (m, 1H), 6.98–6.92 (m, 2H), 2.39 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.9, 159.4 (d, *J*<sub>CF</sub> = 242.4 Hz), 149.8, 148.0, 137.6, 131.8 (d, *J*<sub>CF</sub> = 2.6 Hz), 130.9 (d, *J*<sub>CF</sub> = 7.7 Hz), 126.4, 123.2 (d, *J*<sub>CF</sub> = 8.1 Hz), 122.3, 116.9 (d, *J*<sub>CF</sub> = 22.1 Hz), 113.1 (d, *J*<sub>CF</sub> = 20.9 Hz), 17.8.

*N*-(5-Fluoro-2-methylphenyl)picolinamide<sup>11</sup> (**1k**): white solid (3.53 g, 77% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.17 (s, 1H), 8.62 (d, *J* = 4.0 Hz, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 8.23 (dd, *J* = 10.8 Hz, *J* = 2.8 Hz, 1H), 7.93–7.90 (m, 1H), 7.51–7.48 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.78–6.74 (m, 1H), 2.38 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 161.8, 161.4 (d, *J*<sub>CF</sub> = 241.0 Hz), 149.6, 148.0, 137.7, 136.9 (d, *J*<sub>CF</sub> = 10.6 Hz), 130.8 (d, *J*<sub>CF</sub> = 8.8 Hz), 126.5, 122.4 (d, *J*<sub>CF</sub> = 3.5 Hz), 122.3, 110.6 (d, *J*<sub>CF</sub> = 21.4 Hz), 107.8 (d, *J*<sub>CF</sub> = 27.1 Hz), 16.9.

**Representative Procedure for the Preparation of (1l).** 1-(4-Methyl-3-nitrophenyl)ethanone (10 mmol, 1.80g, 1 equiv) and Pd/C (129 mg, 0.1 equiv) were dissolved in ethanol (30 mL) with a balloon filled with hydrogen. The resulting mixture was stirred at ambient temperature for 2 h. The reaction solution was evaporated under reduced pressure. Compound **1l** was purposely synthesized by condensation with 1-(3-amino-4-methylphenyl)ethanone and picolinic acid (12 mmol, 1.56g, 1.2 equiv).

*N*-(5-Acetyl-2-methylphenyl)picolinamide (**1l**): white solid (1.83 g, 72% yield); mp 105–107 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) using the general procedures above. δ 10.22 (s, 1H), 8.90 (d, *J* = 1.6 Hz, 1H), 8.66 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.97 (t, *J* = 7.6 Hz, 1H), 7.73 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 6.4 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 2.65 (s, 3H), 2.49 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 197.9, 161.9, 149.4, 147.9, 138.3, 136.1, 136.0, 133.8, 130.8, 126.8, 124.2, 122.7, 121.8, 26.8, 18.1. HRMS (EI) calcd for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 254.1055, found 254.1054; IR (neat, cm<sup>-1</sup>) ν 3442, 3343, 2996, 1693, 1675, 1580, 1228, 1040, 748, 687.

*Methyl 3-methyl-4-(picolinamido)benzoate (1m)*: white solid (3.4 g, 63% yield); mp 128–130 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.34 (s, 1H), 8.64 (d, *J* = 4.8 Hz, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.94–7.92 (m, 3H), 7.51 (td, *J* = 4.8 Hz, *J* = 1.2 Hz, 1H), 3.91 (s, 3H), 2.48 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 166.9, 161.9, 149.7, 148.2, 140.3, 137.8, 131.8, 128.8, 126.8, 126.9, 125.4, 122.5, 119.6, 51.9, 17.6; HRMS (EI) calcd for C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 270.1004, found 270.1007; IR (neat, cm<sup>-1</sup>) ν 3432, 3341, 2948, 1733, 1683, 1508, 1207, 991, 748, 671.

**Representative Procedure for the Preparation of (1n).** A copper-catalyzed sulfonylation was used to install the methyl sulfone group to afford 2-methyl-4-(methylsulfonyl)aniline.<sup>20</sup> Then the aniline (5 mmol, 925 mg, 1 equiv) and picolinic acid (6 mmol, 738 mg, 1.2 equiv) were synthesized (**1n**) using the general procedure described above.

*N*-(2-Methyl-4-(methylsulfonyl)phenyl)picolinamide (**1n**): white solid (1.02 g, 70% yield); mp 165–167 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.43 (s, 1H), 8.68–8.65 (m, 2H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.96 (t, *J* = 6.8 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 1H), 7.57–7.54 (m, 1H), 3.07 (s, 3H), 2.52 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>) δ 162.1, 149.2, 148.2, 140.9, 138.0, 135.0, 129.3, 128.0, 127.1, 126.7, 122.7, 120.3, 44.8, 17.6. HRMS (EI) calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S (M<sup>+</sup>) 290.0725, found 290.0729; IR (neat, cm<sup>-1</sup>) ν 3442, 3285, 2927, 1744, 1696, 1580, 1531, 1218, 1134, 958, 771.

*N*-(2-Methyl-4-nitrophenyl)picolinamide<sup>11</sup> (**1o**): white solid (3.27 g, 64% yield); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>) δ 10.28 (s, 1H), 9.27 (s, 1H), 8.63 (d, *J* = 4.0 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.97–7.91 (m, 2H), 7.56–7.53 (m, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 2.52 (s,

3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  162.0, 149.1, 148.1, 146.9, 137.8, 136.6, 134.6, 130.7, 126.9, 122.4, 118.8, 115.4, 17.9.

**N-(2-Methylnaphthalen-1-yl)picolinamide (1p)**: white solid (3.74 g, 71% yield); mp 166–168 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  9.89 (s, 1H), 8.70–8.68 (m, 1H), 8.34 (d,  $J$  = 8.0 Hz, 1H), 7.95–7.91 (m, 2H), 7.85–7.83 (m, 1H), 7.76 (d,  $J$  = 8.4 Hz, 1H), 7.54–7.51 (m, 1H), 7.50–7.41 (m, 3H), 2.48 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  163.0, 149.8, 148.3, 137.7, 133.2, 132.8, 130.6, 129.8, 128.9, 128.2, 127.5, 126.6, 125.3, 122.8, 122.5, 18.9. HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$  ( $M^+$ ) 262.1106, found 262.1109; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3456, 3319, 2919, 1680, 1499, 1430, 1280, 1038, 818, 612.

**N-o-Tolylquinoline-2-carboxamide<sup>21</sup> (3a)**: white solid (4.22 g, 81% yield);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.33 (s, 1H), 8.39 (d,  $J$  = 8.4 Hz, 1H), 8.35–8.32 (m, 2H), 8.13 (d,  $J$  = 8.4 Hz, 1H), 7.88 (d,  $J$  = 8.4 Hz, 1H), 7.80–7.75 (m, 1H), 7.62 (t,  $J$  = 8.0 Hz, 1H), 7.30 (t,  $J$  = 7.6 Hz, 1H), 7.52–7.23 (m, 1H), 7.11–7.07 (m, 1H), 2.48 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.9, 149.8, 146.2, 137.7, 135.9, 130.4, 130.2, 129.7, 129.3, 128.0, 127.9, 127.7, 126.9, 124.4, 121.1, 118.6, 17.6.

**N-(2,5-Dimethylphenyl)quinoline-2-carboxamide<sup>19</sup> (3b)**: white solid (3.95 g, 72% yield);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.31 (s, 1H), 8.38 (q,  $J$  = 8.4 Hz, 2H), 8.18–8.14 (m, 2H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 7.79 (t,  $J$  = 7.6 Hz, 1H), 7.64 (t,  $J$  = 7.6 Hz, 1H), 7.13 (d,  $J$  = 7.6 Hz, 1H), 6.91 (d,  $J$  = 7.2 Hz, 1H), 2.45 (s, 3H), 2.39 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.8, 149.9, 146.1, 137.8, 136.6, 135.7, 130.2, 129.7, 129.3, 128.0, 127.7, 125.2, 124.8, 121.6, 118.8, 20.9, 17.7.

**N-(2,4-Dimethylphenyl)quinoline-2-carboxamide (3c)**: white solid (4.19 g, 76% yield); mp 103–105 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.31 (s, 1H), 8.38 (q,  $J$  = 8.4 Hz, 2H), 8.18–8.14 (m, 2H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 7.79 (t,  $J$  = 7.6 Hz, 1H), 7.64 (t,  $J$  = 7.6 Hz, 1H), 7.13 (d,  $J$  = 7.6 Hz, 1H), 6.91 (d,  $J$  = 7.2 Hz, 1H), 2.45 (s, 3H), 2.39 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.9, 150.1, 146.3, 137.8, 134.3, 133.4, 131.2, 130.3, 129.8, 129.4, 128.3, 128.1, 127.8, 127.4, 121.5, 118.8, 20.9, 17.7; HRMS (EI) calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$  ( $M^+$ ) 276.1263, found 276.1260.

**N-(2,3-Dimethylphenyl)quinoline-2-carboxamide<sup>19</sup> (3d)**: white solid (3.85 g, 70% yield);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.31 (s, 1H), 8.32 (q,  $J$  = 8.4 Hz, 2H), 8.15 (d,  $J$  = 8.8 Hz, 1H), 8.04 (d,  $J$  = 8.0 Hz, 1H), 7.89 (d,  $J$  = 8.0 Hz, 1H), 7.78 (t,  $J$  = 8.0 Hz, 1H), 7.62 (d,  $J$  = 7.6 Hz, 1H), 7.24–7.17 (m, 1H), 7.02 (d,  $J$  = 7.6 Hz, 1H), 2.35 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  162.2, 150.1, 146.3, 137.8, 137.3, 135.7, 130.3, 129.8, 129.4, 128.1, 127.8, 127.7, 126.8, 126.1, 120.1, 118.8, 20.8, 17.6.

**N-(4-Iodo-2-methylphenyl)quinoline-2-carboxamide (3e)**: white solid (4.81 g, 62% yield); mp 148–150 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.31 (s, 1H), 8.39–8.34 (m, 2H), 8.30 (d,  $J$  = 8.8 Hz, 1H), 8.14 (d,  $J$  = 8.4 Hz, 1H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 7.80 (t,  $J$  = 8.0 Hz, 1H), 7.65 (t,  $J$  = 8.0 Hz, 1H), 7.26–7.23 (m, 2H), 2.46 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.8, 149.4, 146.1, 138.9, 137.9, 135.8, 130.3, 129.9, 129.7, 129.4, 128.2, 127.7, 122.5, 118.6, 88.0, 17.2; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{13}\text{IN}_2\text{O}$  ( $M^+$ ) 388.0073, found 388.0072.

**N-(4-Bromo-2-methylphenyl)quinoline-2-carboxamide (3f)**: white solid (4.47 g, 66% yield); mp 155–157 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 8.39–8.35 (m, 2H), 8.26 (d,  $J$  = 8.4 Hz, 1H), 8.14 (d,  $J$  = 8.8 Hz, 1H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 7.80 (t,  $J$  = 8.0 Hz, 1H), 7.65 (t,  $J$  = 7.6 Hz, 1H), 7.39 (m, 2H), 2.45 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.8, 149.4, 146.1, 137.8, 135.0, 132.9, 130.3, 129.8, 129.7, 129.6, 129.4, 128.2, 127.7, 122.3, 118.5, 116.9, 17.4; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}$  ( $M^+$ ) 340.0211, found 340.0223.

**N-(4-Chloro-2-methylphenyl)quinoline-2-carboxamide (3g)**: white solid (3.87 g, 65% yield); mp 138–140 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 8.39–8.34 (m, 2H), 8.30 (d,  $J$  = 8.8 Hz, 1H), 8.14 (d,  $J$  = 8.4 Hz, 1H), 7.90 (d,  $J$  = 8.4 Hz, 1H), 7.80 (t,  $J$  = 8.0 Hz, 1H), 7.65 (t,  $J$  = 8.0 Hz, 1H), 7.26–7.23 (m, 2H), 2.46 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.9, 149.5, 146.1, 137.8, 134.5, 130.3, 130.1, 129.7, 129.6, 129.4, 129.2, 128.2,

127.7, 126.8, 122.1, 118.6, 17.5; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}$  ( $M^+$ ) 296.0716, found 296.0721.

**N-(5-Fluoro-2-methylphenyl)quinoline-2-carboxamide (3h)**: white solid (4.17 g, 74% yield); mp 116–118 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.44 (s, 1H), 8.32 (m, 2H), 8.15 (dd,  $J$  = 10.8 Hz, 2.4 Hz, 1H), 8.15 (d,  $J$  = 8.4 Hz, 1H), 7.91 (d,  $J$  = 7.6 Hz, 1H), 7.80 (t,  $J$  = 8.0 Hz, 1H), 7.66 (d,  $J$  = 8.0 Hz, 1H), 7.17 (t,  $J$  = 7.6 Hz, 1H), 6.79 (dt,  $J$  = 8.0 Hz, 2.8 Hz, 1H), 2.47 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.5, 161.1 (d,  $J_{\text{CF}}$  = 191.4 Hz), 149.0, 145.7, 137.5, 136.5 (d,  $J_{\text{CF}}$  = 9.5 Hz), 130.5 (d,  $J_{\text{CF}}$  = 7.6 Hz), 129.9, 129.3, 129.0, 127.8, 127.3, 122.0 (d,  $J_{\text{CF}}$  = 3.4 Hz), 118.3, 110.2 (d,  $J_{\text{CF}}$  = 16.0 Hz), 107.3 (d,  $J_{\text{CF}}$  = 20.5 Hz), 16.5; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}$  ( $M^+$ ) 280.1012, found 280.1010.

**N-(4-Fluoro-2-methylphenyl)quinoline-2-carboxamide (3i)**: white solid (3.97 g, 71% yield); mp 105–107 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.21 (s, 1H), 8.40–8.34 (m, 2H), 8.21–8.19 (m, 1H), 8.14 (d,  $J$  = 8.4 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.80 (t,  $J$  = 8.0 Hz, 1H), 7.64 (t,  $J$  = 7.2 Hz, 1H), 7.00–6.96 (m, 2H), 2.46 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  161.9, 159.4 (d,  $J_{\text{CF}}$  = 242.3 Hz), 149.6, 146.1, 137.8, 131.8 (d,  $J_{\text{CF}}$  = 2.2 Hz), 130.9 (d,  $J_{\text{CF}}$  = 8.1 Hz), 130.2, 129.7, 129.3, 128.1, 127.7, 123.1 (d,  $J_{\text{CF}}$  = 8.1 Hz), 118.6, 116.9 (d,  $J_{\text{CF}}$  = 22.5 Hz), 113.2 (d,  $J_{\text{CF}}$  = 21.7 Hz), 17.8; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}$  ( $M^+$ ) 280.1012, found 280.1015.

**Methyl 3-methyl-4-(quinoline-2-carboxamido)benzoate (3j)**: white solid (4.6 g, 72% yield); mp 134–136 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.57 (s, 1H), 8.57 (d,  $J$  = 8.4 Hz, 1H), 8.37 (s, 2H), 8.14 (d,  $J$  = 8.4 Hz, 1H), 7.98–7.89 (m, 3H), 7.81 (t,  $J$  = 7.6 Hz, 1H), 7.65 (t,  $J$  = 7.6 Hz, 1H), 3.91 (s, 3H), 2.55 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  166.9, 162.1, 149.5, 146.2, 140.3, 138.0, 131.8, 130.4, 129.8, 129.6, 128.9, 128.4, 127.8, 126.7, 125.4, 119.5, 118.7, 51.9, 17.6; HRMS (EI) calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$  ( $M^+$ ) 320.1161, found 320.1165; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3445, 3330, 2927, 1701, 1536, 1492, 1295, 914, 770, 693.

**Typical Experimental Procedure for the Oxidative Acetylation of Benzylic C–H Bonds.** A flask with a magnetic stir bar was charged with picolinamide (0.3 mmol),  $\text{PhI}(\text{OAc})_2$  (146 mg, 0.45 mmol),  $\text{Pd}(\text{OAc})_2$  (4 mg, 0.015 mmol),  $\text{HOAc}/\text{Ac}_2\text{O}$  (18 mg/31 mg, 0.3 mmol/0.3 mmol), and toluene (2 mL). The mixture was stirred for 30 min at room temperature and then heated at 130 °C in an oil bath for 12 h under air. Afterward, the reaction mixture was allowed to cool to room temperature. Water was added, and the mixture was extracted with ethyl acetate. The combined organic layers was washed with brine water, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo. The residue was purified by silica gel flash chromatography to give the desired product.

**Characterization Data of the Products.** **2-(Picolinamido)benzyl acetate (2a)**: white solid (64 mg, 79% yield); mp 94–96 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.63 (s, 1H), 8.61 (d,  $J$  = 4.0 Hz, 1H), 8.31 (d,  $J$  = 8.0 Hz, 2H), 7.92 (t,  $J$  = 7.6 Hz, 1H), 7.51–7.48 (m, 1H), 7.46–7.42 (m, 1H), 7.37 (d,  $J$  = 7.6 Hz, 1H), 7.17 (t,  $J$  = 7.2 Hz, 1H), 5.21 (s, 2H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.7, 162.3, 149.8, 148.0, 137.6, 136.7, 130.3, 129.8, 126.5, 125.8, 124.5, 122.5, 122.4, 64.5, 20.8; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$  ( $M^+$ ) 270.1004, found 270.1008; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3435, 3351, 2963, 1743, 1687, 1529, 1213, 996, 762, 679.

**4-Methyl-2-(picolinamido)benzyl acetate (2b)**: white solid (62 mg, 73% yield); mp 96–98 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.58 (s, 1H), 8.61 (d,  $J$  = 4.0 Hz, 1H), 8.30 (d,  $J$  = 8.0 Hz, 1H), 8.15 (s, 1H), 7.92 (t,  $J$  = 7.6 Hz, 1H), 7.51–7.47 (m, 1H), 7.27–7.24 (m, 1H), 6.98 (d,  $J$  = 7.2 Hz, 1H), 5.17 (s, 2H), 2.41 (s, 3H), 2.19 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.8, 162.2, 149.9, 148.0, 139.9, 137.6, 136.6, 130.2, 126.4, 125.3, 123.0, 122.9, 122.4, 64.3, 21.4, 20.8; HRMS (EI) calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$  ( $M^+$ ) 284.1161, found 284.1163; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3454, 3349, 2964, 1749, 1691, 1532, 1241, 998, 746, 676.

**5-Methyl-2-(picolinamido)benzyl acetate (2c)**: white solid (58 mg, 68% yield); mp 80–82 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.55 (s, 1H), 8.61 (d,  $J$  = 3.6 Hz, 1H), 8.30 (d,  $J$  = 7.6 Hz, 1H), 8.15 (s, 1H), 7.91 (t,  $J$  = 7.6 Hz, 1H), 7.51–7.47 (m, 1H), 7.26–7.24 (m, 1H), 6.98 (d,  $J$  = 6.8 Hz, 1H), 5.17 (s, 2H), 2.41 (s, 3H), 2.19



(s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.8, 162.2, 149.9, 148.0, 139.9, 137.6, 136.6, 130.2, 126.4, 125.3, 123.0, 122.9, 122.4, 64.3, 21.4, 20.8; HRMS (EI) calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ) 284.1161, found 284.1167; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3442, 3351, 2958, 1747, 1683, 1527, 1217, 996, 753, 673.

**2-Methyl-6-(picolinamido)benzyl acetate (2d)**: white solid (63 mg, 74% yield); mp 60–62 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.75 (s, 1H), 8.61 (d,  $J = 4.0$  Hz, 1H), 8.30 (d,  $J = 8.0$  Hz, 1H), 7.99 (d,  $J = 8.4$  Hz, 1H), 7.90 (t,  $J = 7.6$  Hz, 1H), 7.49–7.46 (m, 1H), 7.32 (t,  $J = 7.6$  Hz, 1H), 7.05 (d,  $J = 7.6$  Hz, 1H), 5.26 (s, 2H), 2.46 (s, 3H), 2.17 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  171.2, 162.6, 150.0, 148.1, 138.4, 137.5, 137.1, 129.2, 127.0, 126.3, 125.2, 122.5, 121.4, 60.4, 20.8, 19.6; HRMS (EI) calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ) 284.1161, found 284.1164; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3455, 3335, 2938, 1742, 1692, 1545, 1218, 1022, 729, 688.

**4-(Picolinamido)biphenyl-3-yl)methyl acetate (2f)**: white solid (78 mg, 75% yield); mp 107–109 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.67 (s, 1H), 8.62 (d,  $J = 3.6$  Hz, 1H), 8.41 (d,  $J = 8.4$  Hz, 1H), 8.32 (d,  $J = 8.0$  Hz, 1H), 7.92 (dt,  $J = 7.6$  Hz,  $J = 1.6$  Hz, 1H), 7.67 (dd,  $J = 8.4$  Hz,  $J = 2.0$  Hz, 1H), 7.61–7.59 (m, 3H), 7.51–7.42 (m, 3H), 7.36–7.32 (m, 1H), 5.27 (s, 3H), 2.22 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.8, 162.4, 149.9, 148.1, 140.2, 137.7, 137.5, 136.1, 129.0, 128.7, 128.4, 127.4, 127.0, 126.6, 126.2, 122.8, 122.6, 64.7, 20.9; HRMS (EI) calcd for  $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ) 346.1317, found 346.1309; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3458, 3344, 2983, 1743, 1688, 1519, 1495, 1220, 1019, 771, 675.

**5-Iodo-2-(picolinamido)benzyl acetate (2g)**: white solid (84 mg, 71% yield); mp 128–130 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.61 (s, 1H), 8.61 (d,  $J = 4.4$  Hz, 1H), 8.29 (d,  $J = 8.0$  Hz, 1H), 8.11 (d,  $J = 8.8$  Hz, 1H), 7.92 (t,  $J = 8.0$  Hz, 1H), 7.73–7.69 (m, 2H), 7.51 (t,  $J = 4.8$  Hz, 1H), 5.14 (s, 2H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.5, 162.2, 149.5, 148.1, 138.7, 138.5, 137.7, 136.6, 127.8, 126.6, 123.9, 122.5, 87.8, 63.4, 20.8; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{13}\text{IN}_2\text{O}_3$  ( $\text{M}^+$ ) 395.9971, found 395.9968; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3451, 3324, 2973, 1735, 1690, 1522, 1261, 1021, 749, 688.

**5-Bromo-2-(picolinamido)benzyl acetate (2h)**: white solid (75 mg, 72% yield); mp 131–133 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.60 (s, 1H), 8.61 (d,  $J = 3.6$  Hz, 1H), 8.28 (d,  $J = 8.0$  Hz, 1H), 8.22 (d,  $J = 8.8$  Hz, 1H), 7.92 (t,  $J = 7.2$  Hz, 1H), 7.54–7.50 (m, 3H), 5.16 (s, 2H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.5, 162.2, 149.5, 148.1, 137.7, 135.8, 132.8, 132.5, 127.8, 126.6, 123.8, 122.5, 117.1, 63.5, 20.7; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{13}\text{BrN}_2\text{O}_3$  ( $\text{M}^+$ ) 348.0110, found 348.0111; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3353, 3326, 2968, 1735, 1690, 1527, 1263, 1030, 748, 686.

**5-Chloro-2-(picolinamido)benzyl acetate (2i)**: white solid (69 mg, 76% yield); mp 127–129 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.79 (s, 1H), 8.61 (d,  $J = 3.6$  Hz, 1H), 8.28 (t,  $J = 8.8$  Hz, 2H), 7.92 (t,  $J = 7.2$  Hz, 1H), 7.52–7.49 (m, 1H), 7.40–7.36 (m, 2H), 5.16 (s, 2H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.5, 162.3, 149.5, 148.1, 137.7, 135.2, 129.9, 129.5, 127.6, 126.6, 123.6, 122.5, 63.6, 20.7; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{13}\text{ClN}_2\text{O}_3$  ( $\text{M}^+$ ) 304.0615, found 304.0624; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3446, 3343, 3060, 1742, 1686, 1526, 1244, 1029, 748, 676.

**5-Fluoro-2-(picolinamido)benzyl acetate (2j)**: white solid (42 mg, 49% yield); mp 114–116 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.49 (s, 1H), 8.61 (d,  $J = 4.4$  Hz, 1H), 8.29 (d,  $J = 8.0$  Hz, 1H), 8.19–8.15 (m, 1H), 7.92 (t,  $J = 8.0$  Hz, 1H), 7.52–7.49 (m, 1H), 7.14–7.10 (m, 2H), 5.16 (s, 2H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.5, 162.4, 159.3 (d,  $J_{\text{CF}} = 243.8$  Hz), 149.6, 148.1, 137.6, 132.4 (d,  $J_{\text{CF}} = 2.7$  Hz), 128.6 (d,  $J_{\text{CF}} = 8.1$  Hz), 126.5, 124.6 (d,  $J_{\text{CF}} = 7.0$  Hz), 122.5, 116.7 (d,  $J_{\text{CF}} = 22.5$  Hz), 116.04 (d,  $J_{\text{CF}} = 22.6$  Hz), 63.5, 20.7; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}_3$  ( $\text{M}^+$ ) 288.0910, found 288.0909; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3451, 3334, 2969, 1740, 1690, 1538, 1259, 1030, 749, 683.

**4-Fluoro-2-(picolinamido)benzyl acetate (2k)**: white solid (68 mg, 79% yield); mp 125–127 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.73 (s, 1H), 8.61 (d,  $J = 4.8$  Hz, 1H), 8.30 (d,  $J = 8.4$  Hz, 1H), 8.24–8.21 (m, 1H), 7.94 (t,  $J = 8.0$  Hz, 1H), 7.53–7.50 (m, 1H), 7.34–7.31 (m, 1H), 6.85 (dt,  $J = 8.4$  Hz, 2.4 Hz), 5.12 (s, 2H), 2.20 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.7, 163.2

(d,  $J_{\text{CF}} = 244.7$  Hz), 162.2, 149.4, 148.1, 138.4 (d,  $J_{\text{CF}} = 16.9$  Hz), 137.7, 131.2 (d,  $J_{\text{CF}} = 10.5$  Hz), 126.7, 122.5, 120.9 (d,  $J_{\text{CF}} = 2.8$  Hz), 110.9 (d,  $J_{\text{CF}} = 22.0$  Hz), 109.2 (d,  $J_{\text{CF}} = 27.5$  Hz), 63.8, 20.8; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}_3$  ( $\text{M}^+$ ) 288.0910, found 288.0908; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3465, 3323, 2917, 1746, 1695, 1537, 1224, 1007, 750, 690.

**4-Acetyl-2-(picolinamido)benzyl acetate (2l)**: white solid (58 mg, 62% yield); mp 127–129 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.69 (s, 1H), 8.91 (d,  $J = 1.2$  Hz, 1H), 8.63 (d,  $J = 4.0$  Hz, 1H), 8.33 (d,  $J = 8.0$  Hz, 1H), 7.95 (dt,  $J = 8.0$  Hz,  $J = 1.6$  Hz, 1H), 7.79 (dd,  $J = 8.0$  Hz,  $J = 1.6$  Hz, 1H), 7.55–7.51 (m, 1H), 7.48 (d,  $J = 8.0$  Hz, 1H), 5.24 (s, 2H), 2.67 (s, 3H), 2.22 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  197.6, 170.6, 162.6, 149.6, 148.2, 138.2, 137.8, 137.1, 130.6, 130.4, 126.8, 124.1, 122.7, 122.6, 64.9, 26.9, 20.8. HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ) 312.1110, found 312.1107; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3442, 3321, 2921, 1742, 1686, 1582, 1537, 1236, 1026, 749, 688.

**Methyl 3-(acetoxymethyl)-4-(picolinamido)benzoate (2m)**: white solid (63 mg, 65% yield); mp 145–147 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.84 (s, 1H), 8.62 (d,  $J = 4.0$  Hz, 1H), 8.54 (d,  $J = 8.4$  Hz, 1H), 8.32 (d,  $J = 4.0$  Hz, 1H), 8.11 (dd,  $J = 8.8$  Hz,  $J = 2.0$  Hz, 1H), 8.06 (m, 1H), 7.94 (dt,  $J = 7.6$  Hz,  $J = 1.2$  Hz, 1H), 7.53–7.51 (m, 1H), 5.26 (s, 2H), 3.92 (s, 3H), 2.22 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.6, 166.3, 162.4, 149.5, 148.2, 141.1, 137.8, 131.9, 131.4, 126.9, 125.7, 125.0, 122.7, 121.2, 64.2, 51.1, 20.8; HRMS (EI) calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_5$  ( $\text{M}^+$ ) 328.1059, found 328.1057; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3454, 3305, 2924, 1741, 1689, 1528, 1286, 961, 722, 690.

**N-(2-Methyl-4-(methylsulfonyl)phenyl)picolinamide (2n)**: white solid (61 mg, 59% yield); mp 152–154 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.92 (s, 1H), 8.69 (d,  $J = 8.4$  Hz, 1H), 8.64 (s, 1H), 8.32 (t,  $J = 7.6$  Hz, 1H), 8.01–7.95 (m, 3H), 7.57–7.54 (m, 1H), 5.27 (s, 2H), 3.08 (s, 3H), 2.23 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.5, 162.7, 149.1, 148.2, 141.9, 138.0, 135.4, 129.5, 129.3, 127.2, 126.0, 122.8, 120.0, 63.7, 44.7, 20.8. HRMS (EI) calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5\text{S}$  ( $\text{M}^+$ ) 348.0780, found 348.0780; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3345, 3324, 2922, 1696, 1690, 1579, 1536, 1297, 1129, 976, 762, 679.

**5-Nitro-2-(picolinamido)benzyl acetate (2o)**: white solid (40 mg, 49% yield); mp 183–185 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.80 (s, 1H), 9.28 (d,  $J = 1.6$  Hz, 1H), 8.64 (d,  $J = 4.8$  Hz, 1H), 8.33 (d,  $J = 7.6$  Hz, 1H), 8.01 (dd,  $J = 8.4$  Hz, 2.0 Hz, 1H), 7.99–7.95 (m, 1H), 7.56–7.54 (m, 2H), 5.28 (s, 2H), 2.34 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.4, 162.5, 149.9, 148.6, 148.1, 137.8, 137.7, 131.7, 130.6, 127.0, 122.7, 118.9, 116.9, 63.3, 20.7; HRMS (EI) calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_5$  ( $\text{M}^+$ ) 315.0855, found 315.0861; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3481, 3329, 2918, 1752, 1693, 1536, 1236, 1010, 751, 689.

**7-Methyl-8-(picolinamido)naphthalen-1-yl acetate (2p)**: white solid (52 mg, 54% yield); mp 158–160 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  9.84 (s, 1H), 8.69 (d,  $J = 4.4$  Hz, 1H), 8.33 (d,  $J = 7.6$  Hz, 1H), 7.96–7.92 (m, 2H), 7.85 (d,  $J = 9.6$  Hz, 1H), 7.55–7.46 (m, 3H), 7.23 (s, 1H), 2.45 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  169.5, 163.1, 149.6, 148.2, 145.6, 137.7, 133.4, 131.6, 128.0, 127.2, 126.7, 126.0, 125.8, 123.0, 122.8, 121.5, 120.9, 21.1, 18.9; HRMS (EI) calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ) 320.1161, found 320.1166; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3442, 3283, 2927, 1744, 1695, 1580, 1583, 1218, 1133, 958, 771.

**2-(Quinoline-2-carboxamido)benzyl acetate (4a)**: white solid (62 mg, 65% yield); mp 143–145 °C (uncorrected);  $^1\text{H}$  NMR (400 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  10.80 (s, 1H), 8.42–8.36 (m, 3H), 8.13 (d,  $J = 8.4$  Hz, 1H), 7.91 (t,  $J = 8.0$  Hz, 1H), 7.81 (t,  $J = 7.2$  Hz, 1H), 7.65 (t,  $J = 7.2$  Hz, 1H), 7.47 (t,  $J = 7.6$  Hz, 1H), 7.41 (d,  $J = 8.0$  Hz, 1H), 7.19 (t,  $J = 7.6$  Hz, 1H), 5.30 (s, 2H), 2.22 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, TMS,  $\text{CDCl}_3$ )  $\delta$  170.8, 162.4, 149.6, 146.3, 137.8, 136.9, 130.5, 130.3, 129.9, 129.6, 129.4, 128.2, 127.8, 125.7, 124.5, 122.1, 118.7, 64.4, 21.0; HRMS (EI) calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$  ( $\text{M}^+$ ) 320.1161, found 320.1165; IR (neat,  $\text{cm}^{-1}$ )  $\nu$  3441, 3320, 2919, 1741, 1685, 1533, 1227, 1022, 760, 692.

**4-Methyl-2-(quinoline-2-carboxamido)benzyl acetate (4b)**: white solid (67 mg, 67% yield); mp 105–107 °C (uncorrected);  $^1\text{H}$  NMR

(400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.76 (s, 1H), 8.41–8.35(m, 2H), 8.25 (s, 1H), 8.13 (d,  $J$  = 8.8 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.80 (t,  $J$  = 7.6 Hz, 1H), 7.65 (t,  $J$  = 7.2 Hz, 1H), 7.28(d,  $J$  = 7.6 Hz, 1H), 6.99 (d,  $J$  = 7.6 Hz, 1H), 5.27 (s, 2H), 2.24 (s, 3H), 2.21 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.8, 162.3, 149.7, 146.3, 140.0, 137.8, 136.7, 130.5, 130.3, 129.6, 129.4, 128.1, 127.7, 125.2, 122.8, 122.7, 118.7, 64.2, 21.0, 20.1; HRMS (EI) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 334.1317, found 334.1312; IR (neat, cm<sup>-1</sup>)  $\nu$  3461, 3332, 2917, 1738, 1690, 1543, 1217, 1024, 775, 694.

**5-Methyl-2-(quinoline-2-carboxamido)benzyl acetate (4c):** white solid (65 mg, 65% yield); mp 137–139 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.70 (s, 1H), 8.40–8.34 (m, 2H), 8.24 (d,  $J$  = 8.0 Hz, 1H), 8.12 (d,  $J$  = 8.4 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.82–7.78 (m, 1H), 7.64 (t,  $J$  = 7.2 Hz, 1H), 7.27–7.22 (m, 2H), 5.26 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.8, 162.3, 149.7, 146.3, 137.7, 134.2, 131.0, 130.3, 130.2, 129.6, 129.3, 128.0, 127.7, 125.8, 122.3, 118.7, 64.3, 21.0, 20.8; HRMS (EI) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 334.1317, found 334.1320; IR (neat, cm<sup>-1</sup>)  $\nu$  3473, 3330, 2920, 1745, 1679, 1532, 1215, 1024, 776, 681.

**2-Methyl-6-(quinoline-2-carboxamido)benzyl acetate (4d):** white solid (64 mg, 64%); mp 80–82 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.97 (s, 1H), 8.41–8.36 (m, 2H), 8.17 (d,  $J$  = 8.4 Hz, 1H), 8.11 (d,  $J$  = 8.0 Hz, 1H), 7.92 (d,  $J$  = 8.4 Hz, 1H), 7.82–7.79 (m, 1H), 7.67–7.64 (m, 1H), 7.35 (t,  $J$  = 7.6 Hz, 1H), 7.07 (d,  $J$  = 7.2 Hz, 1H), 5.36 (s, 2H), 2.49 (s, 3H), 2.21 (s, 3H); <sup>13</sup>C NMR (125 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  171.2, 162.9, 149.9, 146.5, 138.6, 137.8, 137.4, 130.3, 129.8, 129.5, 128.2, 127.8, 127.1, 125.0, 121.1, 118.9, 60.4, 21.1, 19.8. HRMS (EI) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 334.1317, found 334.1320; IR (neat, cm<sup>-1</sup>)  $\nu$  3435, 3314, 2917, 1752, 1695, 1541, 1209, 1023, 770, 738.

**5-Iodo-2-(quinoline-2-carboxamido)benzyl acetate (4e):** white solid (90 mg, 67% yield); mp 166–168 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.78 (s, 1H), 8.36 (s, 2H), 8.19 (d,  $J$  = 8.4 Hz, 1H), 8.11 (d,  $J$  = 8.4 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.81 (t,  $J$  = 7.6 Hz, 1H), 7.73–7.71 (m, 1H), 7.66 (t,  $J$  = 7.6 Hz, 2H), 5.22 (s, 2H), 2.22 (s, 3H). <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.6, 162.3, 149.3, 146.2, 139.0, 138.6, 137.8, 136.6, 130.4, 129.5, 129.4, 128.3, 127.8, 127.7, 123.7, 118.6, 87.6, 63.3, 21.0; HRMS (EI) calcd for C<sub>19</sub>H<sub>15</sub>IN<sub>2</sub>O<sub>3</sub>(M<sup>+</sup>) 446.0127, found, 446.0125; IR (neat, cm<sup>-1</sup>)  $\nu$  3446, 3303, 2979, 1752, 1691, 1521, 1503, 1211, 1006, 772, 623.

**5-Bromo-2-(quinoline-2-carboxamido)benzyl acetate (4f):** white solid (87 mg, 73% yield); mp 153–155 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.78 (s, 1H), 8.37 (s, 2H), 8.30 (d,  $J$  = 9.2 Hz, 1H), 8.12 (d,  $J$  = 8.4 Hz, 1H), 7.91 (d,  $J$  = 8.0 Hz, 1H), 7.81 (t,  $J$  = 7.6 Hz, 1H), 7.66 (t,  $J$  = 7.2 Hz, 2H), 7.55–7.54 (m, 2H), 5.24 (s, 2H), 2.22 (s, 3H). <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.6, 162.4, 149.3, 146.2, 137.9, 135.9, 133.1, 132.6, 130.4, 129.5, 129.4, 128.3, 127.8, 127.6, 123.6, 118.6, 117.0, 63.4, 20.9; HRMS (EI) calcd for C<sub>19</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>3</sub>(M<sup>+</sup>) 398.0266, found 398.0268; IR (neat, cm<sup>-1</sup>)  $\nu$  3455, 3349, 2989, 1736, 1685, 1527, 1502, 1233, 1023, 774, 659.

**5-Chloro-2-(quinoline-2-carboxamido)benzyl acetate (4g):** white solid (68 mg, 64% yield); mp 147–149 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.78 (s, 1H), 8.37–8.34 (m, 3H), 8.13 (d,  $J$  = 8.8 Hz, 1H), 7.91 (d,  $J$  = 8.0 Hz, 1H), 7.81 (t,  $J$  = 8.0 Hz, 1H), 7.66 (t,  $J$  = 7.6 Hz, 1H), 7.41–7.40 (m, 2H), 7.27–7.22 (m, 2H), 5.25 (s, 2H), 2.23 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.8, 162.4, 149.3, 146.2, 137.9, 135.3, 130.4, 130.3, 130.2, 129.6, 129.5, 129.4, 128.2, 127.7, 127.4, 123.4, 118.6, 64.5, 20.9; HRMS (EI) calcd for C<sub>19</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub>(M<sup>+</sup>) 354.0771, found 354.0776; IR (neat, cm<sup>-1</sup>)  $\nu$  3451.2, 3350, 2961, 1736, 1679, 1528, 1502, 1236, 1025, 774, 669.

**4-Fluoro-2-(quinoline-2-carboxamido)benzyl acetate (4h):** white solid (62 mg, 61% yield); mp 121–123 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.90 (s, 1H), 8.39 (s, 2H), 8.31 (dd,  $J$  = 11.2 Hz, 2.4 Hz, 1H), 8.13 (d,  $J$  = 8.4 Hz, 1H), 7.92 (t,  $J$  = 8.0 Hz, 1H), 7.82 (t,  $J$  = 7.2 Hz, 1H), 7.69–7.65 (m, 1H), 7.36 (t,  $J$  = 8.0 Hz, 1H), 6.87 (dt,  $J$  = 8.4 Hz, 2.4 Hz, 1H), 5.28 (s, 2H), 2.22 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.7, 162.4, 163.3 (d,  $J_{CF}$  = 245.7 Hz), 149.2, 146.3, 138.5 (d,  $J_{CF}$  = 11.6 Hz), 137.9, 131.9 (d,  $J_{CF}$  = 9.5 Hz), 130.5, 129.5, 129.4, 128.3, 127.8, 120.8 (d,  $J_{CF}$  = 3.2 Hz) 118.6, 110.7 (d,  $J_{CF}$  = 21.1 Hz), 109.0 (d,  $J_{CF}$  = 26.7 Hz), 63.7, 21.0; HRMS

(EI) calcd for C<sub>19</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub> (M<sup>+</sup>) 338.1067, found 338.1070; IR (neat, cm<sup>-1</sup>)  $\nu$  3445, 3315, 2934, 1751, 1696, 1533, 1504, 1214, 1024, 771, 681.

**5-Fluoro-2-(quinoline-2-carboxamido)benzyl acetate (4i):** white solid (69 mg, 68% yield); mp 122–124 °C (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.68 (s, 1H), 8.39 (s, 2H), 8.27–8.24 (m, 1H), 8.14 (d,  $J$  = 8.8 Hz, 1H), 7.92 (d,  $J$  = 8.4 Hz, 1H), 7.82 (t,  $J$  = 8.4 Hz, 1H), 7.67 (t,  $J$  = 7.6 Hz, 1H), 7.16–7.13 (m, 2H), 5.24 (s, 2H), 2.23 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.7, 162.6, 159.4 (d,  $J_{CF}$  = 194.5 Hz), 149.5, 146.4, 138.0, 132.7 (d,  $J_{CF}$  = 6.3 Hz), 130.5, 129.7, 129.5, 128.7 (d,  $J_{CF}$  = 4.8 Hz), 128.3, 127.9, 124.6 (d,  $J_{CF}$  = 6.3 Hz), 118.8, 117.0 (d,  $J_{CF}$  = 18.4 Hz), 116.3 (d,  $J_{CF}$  = 17.4 Hz), 63.5, 21.0; HRMS (EI) calcd for C<sub>19</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>(M<sup>+</sup>) 338.1067, found 338.1065; IR (neat, cm<sup>-1</sup>)  $\nu$  3473, 3319, 2953, 1745, 1684, 1532, 1505, 1222, 1023, 778, 688.

**Methyl 3-(acetoxymethyl)-4-(quinoline-2-carboxamido)benzoate (4j):** white solid (64 mg, 57% yield); mp (°C) 145–147 (uncorrected); <sup>1</sup>H NMR (400 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  11.01 (s, 1H), 8.62 (d,  $J$  = 8.4 Hz, 1H), 8.39 (s, 2H), 8.15–8.10 (m, 3H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.83 (t,  $J$  = 7.2 Hz, 1H), 7.67 (t,  $J$  = 6.8 Hz, 1H), 5.35 (s, 3H), 3.93 (s, 3H), 2.22 (s, 3H); <sup>13</sup>C NMR (100 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  170.7, 166.3, 162.6, 149.3, 146.3, 141.2, 138.1, 132.2, 131.6, 130.6, 129.6, 129.5, 128.5, 127.9, 125.6, 124.9, 120.9, 118.7, 64.1, 52.1, 21.1; HRMS (EI) calcd for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub> (M<sup>+</sup>) 378.1216, found 378.1211; IR (neat, cm<sup>-1</sup>)  $\nu$  3422, 3325, 2927, 1717, 1528, 1282, 1018, 768, 698.

**General Procedure for the Hydrolysis of Amide 2.** 2-(Picolinamido)benzyl acetate (**2a**, 81 mg, 0.3 mmol) was dissolved in a mixture of THF/MeOH/H<sub>2</sub>O (1.5/0.5/0.5 mL); NaOH (48 mg, 1.2 mmol, 4.0 equiv) was then added. The mixture was heated to 50 °C and stirred for 24 h. Water was added, and the mixture was extracted with DCM. The combined organic layers were washed with brine water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The residue was purified by silica gel flash chromatography to give the desired product **7** in 85% yields.<sup>8f</sup>

**(2-Aminophenyl)methanol (7):**<sup>22</sup> white solid (31 mg, 85% yield); <sup>1</sup>H NMR (500 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  10.78 (s, 1H), 7.26–7.25 (m, 1H), 7.13 (t,  $J$  = 8.0 Hz, 1H), 7.05 (d,  $J$  = 7.0 Hz, 1H), 6.73–6.69 (m, 2H), 4.65 (s, 1H), 3.08 (bs, 3H); <sup>13</sup>C NMR (125 MHz, TMS, CDCl<sub>3</sub>)  $\delta$  146.0, 129.4, 129.2, 124.8, 118.3, 116.1, 64.4.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all relevant compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: liuzhanx@zju.edu.cn. Fax: +86-571-87951512. Tel: +86-571-87953253.

\*E-mail: yhzhang@zju.edu.cn. Fax: +86-571-87951512. Tel: +86-571-87953253.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Funding from Zhejiang Province (No. 2011C11097) and NSFC (No. 21072169 and No. 21272205) is highly acknowledged. The work was also supported by the Program for Zhejiang Leading Team of S&T Innovation.

## ■ REFERENCES

- (1) For selected reviews of transition-metal-catalyzed C–H activation, see: (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (b) Whited, M. T.; Grubbs, R. H. *Acc. Chem. Res.* **2009**, *42*, 1607. (c) Parkin, G. *Acc. Chem. Res.* **2009**, *42*,

315. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Bellina, F.; Rossi, R. *Chem. Rev.* **2009**, *110*, 1082. (g) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57. (h) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749. (i) Conejero, S.; Paneque, M.; Poveda, M. L.; Santos, L. L.; Carmona, E. *Acc. Chem. Res.* **2010**, *43*, 572. (j) Mkhali, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (k) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.
- (2) For selected reviews of C–O formation, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
- (3) For oxidative acetoxylation C–H bonds, see: (a) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (d) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 1328. (e) Gu, S.; Chen, C.; Chen, W. *J. Org. Chem.* **2009**, *74*, 7203. (f) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726. (g) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (h) Liu, Q.; Li, G.; Yi, H.; Wu, P.; Liu, J.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 2353. (i) Richter, H.; Beckendorf, S.; Mancheño, O. G. *Adv. Synth. Catal.* **2011**, *353*, 295. (j) Zheng, X.; Song, B.; Xu, B. *Eur. J. Org. Chem.* **2010**, *23*, 4376.
- (4) For examples on C(sp<sup>3</sup>)–H acetoxylation, see: (a) Vedernikov, A. N. *Chem. Commun.* **2009**, 4781. (b) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (c) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.
- (5) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Jiang, H.; Chen, H.; Wang, A.; Liu, X. *Chem. Commun.* **2010**, *46*, 7259. (c) Zhang, J.; Khaskin, E.; Anderson, N. P.; Zavalij, P. Y.; Vedernikov, A. N. *Chem. Commun.* **2008**, *44*, 3625. (d) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (e) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2009**, *12*, 532. (f) Stowers, K. J.; Kubota, A.; Sanford, M. S. *Chem. Sci.* **2012**, *3*, 3192.
- (6) (a) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (b) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387.
- (7) Ren, Z.; Mo, F.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 16991.
- (8) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (d) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (e) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (f) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (g) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124.
- (9) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.
- (10) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724.
- (11) Xie, Y.; Yang, Y.; Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2012**, *14*, 1238.
- (12) (a) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (d) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (e) Yu, M.; Xie, Y.; Li, J.; Zhang, Y. *Adv. Synth. Catal.* **2011**, *353*, 2933. (f) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504. (g) Zhang, L.-S.; Chen, K.; Chen, G.; Li, B.-J.; Luo, S.; Guo, Q.-Y.; Wei, J.-B.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 10.
- (13) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.
- (14) Edmont, D.; Rocher, R.; Plisson, C.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1831.
- (15) (a) Suárez, E.; Rodríguez, M. S.  $\beta$ -Fragmentation of Alkoxy Radicals: Synthetic Applications. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 440–454. (b) Baba, H.; Moriyama, K.; Togo, H. *Tetrahedron Lett.* **2011**, *52*, 4303. (c) Fan, R.; Sun, Y.; Ye, Y. *Org. Lett.* **2011**, *13*, 5174. (d) Jiang, M.; Wei, Y.; Shi, M. *J. Org. Chem.* **2010**, *75*, 2528.
- (16) (a) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5276. (b) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem.—Eur. J.* **2012**, *18*, 5541. (c) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476. (d) Zhang, S.; Luo, F.; Wang, W.; Jia, X.; Hu, M.; Cheng, J. *Tetrahedron Lett.* **2010**, *51*, 3317.
- (17) (a) Zhou, Y.; Zhai, Y.; Ji, X.; Liu, G.; Feng, E.; Ye, D.; Zhao, L.; Jiang, H.; Liu, H. *Adv. Synth. Catal.* **2010**, *352*, 373. (b) Fan, J.; Wan, C.; Sun, G.; Wang, Z. *J. Org. Chem.* **2008**, *73*, 8608. (c) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778. (d) Han, B.; Yang, X.-L.; Wang, C.; Bai, Y.-W.; Pan, T.-C.; Chen, X.; Yu, W. *J. Org. Chem.* **2012**, *77*, 1136.
- (18) Zhao, Z.; Wisnoski, D. D.; O'Brien, J. A.; Lemaire, W.; Williams, D. L., Jr; Jacobson, M. A.; Wittman, M.; Ha, S. N.; Schaffhauser, H.; Sur, C.; Pettibone, D. J.; Duggan, M. E.; Conn, P. J.; Hartman, G. D.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1386.
- (19) Goldfarb, D. S. (University of Rochester) US 20090163545 A1, 2009.
- (20) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696.
- (21) Bobal, P.; Suján, J.; Otevrel, J.; Imramovsky, A.; Padelkova, Z.; Jampilek, J. *Molecules* **2012**, *17*, 1292.
- (22) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548.