JOC The Journal of Organic Chemistry

Article

A Chemoselective N-Arylation Reaction of 2-Aminopyridine Derivatives with Arynes

Bin Cheng, Jian Wei, Bing Zu, Jianfei Zhao, Taimin Wang, Xiaoguang Duan, Renqi Wang, Yun Li, and Hongbin Zhai

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01405 • Publication Date (Web): 15 Aug 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Chemoselective *N*-Arylation Reaction of 2-Aminopyridine Derivatives with Arynes

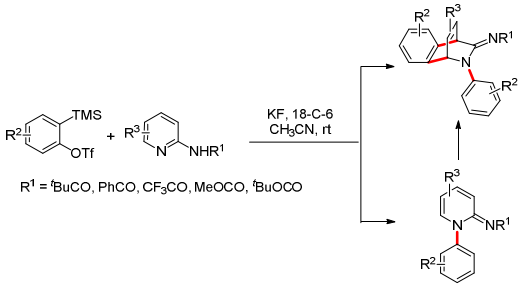
Bin Cheng,[*,†] Jian Wei,[†] Bing Zu,[†] Jianfei Zhao,[†] Taimin Wang,[†] Xiaoguang Duan,[†] Renqi Wang,[†] Yun Li,[†] and Hongbin Zhai[*,†,‡,⊥]

[†] The State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China

[‡] Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China

[⊥] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

Supporting Information Placeholder

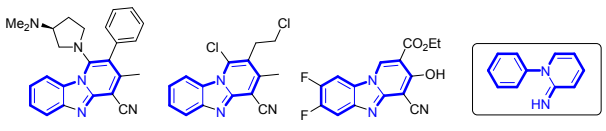


ABSTRACT: A chemoselective *N*-arylation reaction of 2-aminopyridine derivatives with arynes in good to excellent yields has been described. The *N*-arylation products could be further applied to the facile construction of benzoisoquinuclidines and isoquinuclidines as well as pyrido[1,2-*a*]benzimidazoles.

INTRODUCTION

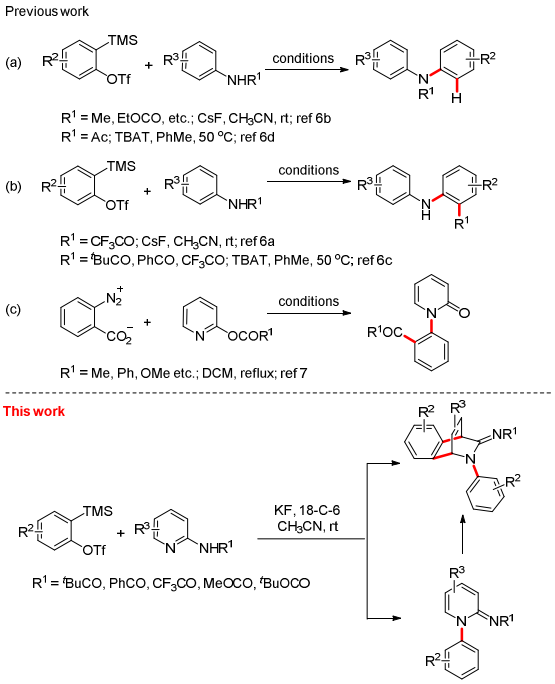
1-Arylpyridin-2(1*H*)-imine motif widely occurs in bioactive molecules and therapeutic agents, for example pyrido[1,2-*a*]benzimidazole derivatives (Figure 1), which have received substantial attention owing to their pronounced pharmaceutical and optical properties.[1] Moreover, it could be a potential Diels-Alder diene partner for the construction of isoquinuclidine framework (i.e., 2-azabicyclo[2.2.2]octane) like its analogue 2-pyridone.[2] However, synthetic approaches to access this unique and simple unit have been rarely developed,[3] as the most straightforward methods involving transition metal mediated C-N bond formation reaction of 2-aminopyrines with aryl halides or aryl boronic acids all afford *N*-arylpyridin-2-amine derivatives as the sole products.[4] Considering the importance of this motif (i.e., 1-arylpyridin-2(1*H*)-imine) and the lack of efficient strategy for its synthesis, we sought to develop a facile protocol utilizing *N*-arylation reaction of 2-aminopyridines with arynes.

Figure 1. Some Pharmaceutical Relevant Pyrido[1,2-*a*]benzimidazole Derivatives



Over the last decades, *o*-(trimethylsilyl)aryl triflate,[5] a new aryne precursor, has attracted much attention from organic chemists, and it has been successfully employed as a reactant in the reaction with a multitude of aniline derivatives.[6] For example, Larock and co-workers, and others have recently accomplished *N*-arylation of anilides with arynes generated from *o*-(trimethylsilyl)aryl triflates as arylation reagents (eq a and b). Moreover, Cheng disclosed the reaction of 2-pyridyl carboxylates with benzynes to form 1-(2-acylphenyl)-2-pyridones (eq c).[7] Indeed, for this challenging *N*-arylation reaction of 2-aminopyridines with arynes, there exist multiple potential side reaction pathways arising from *N*-arylation of the amide, aryne insertion into the amide bond, nucleophilic attack of the pyridino nitrogen on the aryne followed by cyclization with the carbamate,[8] and Diels-Alder reaction of dihydropyridine. Herein, we would like to disclose our results of selective *N*-arylation of 2-aminopyridines with arynes and its application to the syntheses of benzoisoquinuclidines and isoquinuclidines as well as pyrido[1,2-*a*]benzimidazoles (Scheme 1).

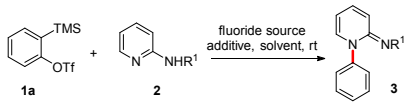
Scheme 1. Reaction of Arylamines with Arynes



RESULTS AND DISCUSSION

Initially, we performed the reaction *o*-(trimethylsilyl)phenyl triflate (**1a**) and 2,2,2-trifluoro-*N*-(pyridin-2-yl)acetamide (**2a**) in the presence of KF/18-Crown-6 in CH_3CN at room temperature (Table 1, entry 1). Delightfully, 75% yield of the desired product **3a** was observed when slight excess of **2a** was used (**1a**:**2a** = 1:1.2) under the reaction conditions. Interestingly, no any side products were detected on TLC. Control experiment carried out in the absence of 18-Crown-6 showed 4% of product formation, which indicates the crucial role of 18-Crown-6 as an additive (entry 2). The replacement of 18-Crown-6 with another additive $BnEt_3NCl$ gave only 35% yield of the product (entry 9). Further enhancement in the yield was observed when the amounts of **2a** was increased to 1.8 equiv (entry 4). However, further increasing the amounts of **2a** or KF/18-Crown-6 (entries 5 and 6) or changing the fluoride source or solvent (entries 7 and 8) did not improve the yields. Unfortunately, the use of free amine (R^1 = H) did not yield any desired product. Moreover, if R^1 was methyl group, *N*-phenylation occurred at the amino group and *N*-methyl-*N*-phenylpyridin-2-amine was isolated as the sole product.

Table 1. Optimization of the Reaction Conditions[a]

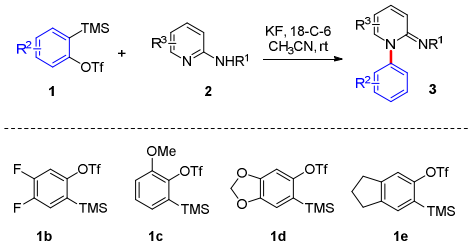


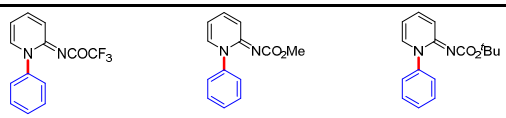
entry	R^1	**1a**:**2**	fluoride source (equiv)	solvent	yield[b] (%)
1	$COCF_3$	1:1.2	KF (2.0)	CH_3CN	75
2[c]	$COCF_3$	1:1.2	KF (2.0)	CH_3CN	4
3	$COCF_3$	1:1.5	KF (2.0)	CH_3CN	88
4	$COCF_3$	1:1.8	KF (2.0)	CH_3CN	89
5	$COCF_3$	1:2.1	KF (2.0)	CH_3CN	89
6[d]	$COCF_3$	1:1.8	KF (3.0)	CH_3CN	85
7	$COCF_3$	1:1.8	KF (2.0)	THF	79
8	$COCF_3$	1:1.8	CsF (2.0)	CH_3CN	79
9[e]	$COCF_3$	1:1.8	KF (2.0)	CH_3CN	35
10	H	1:1.8	KF (2.0)	CH_3CN	*f*
11	Me	1:1.8	KF (2.0)	CH_3CN	*g*

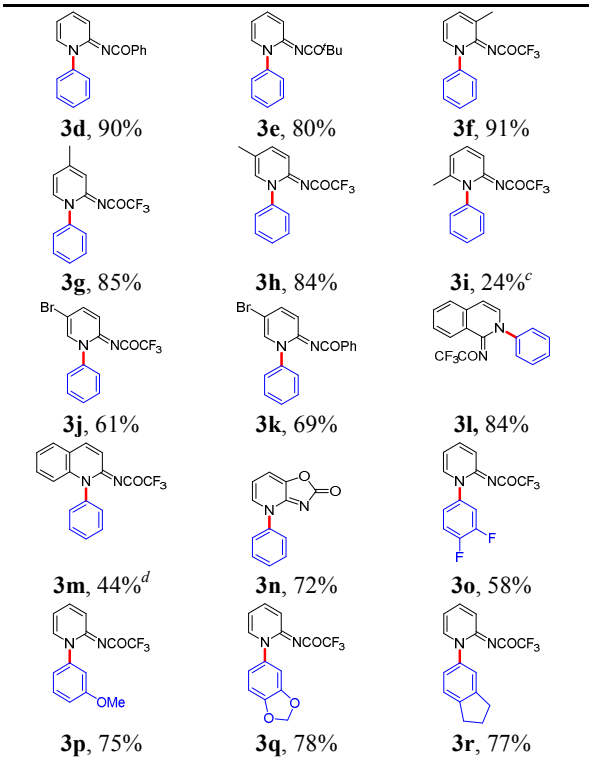
[a]Reaction conditions: **1** (0.3 mmol), **2**, fluoride source (0.6 mmol), 18-Crown-6 (0.6 mmol), solvent (3 mL), rt, air. [b]Isolated yield. [c]Without 18-Crown-6. [d]The amounts of 18-Crown-6 were increased to 3.0 equiv. [e]$BnEt_3NCl$ (2.0 equiv) was used as the additive instead. [f]No desired product was isolated. [g]*N*-Methyl-*N*-phenylpyridin-2-amine was isolated in 56% yield.

When the optimal reaction conditions were determined, we sought to elucidate the scope of this transformation. As presented in Table 2, apart from 2,2,2-trifluoro-*N*-(pyridin-2-yl)acetamide, other acylated 2-aminopyridines proceeded smoothly and formed the corresponding products (**3b**–**3e**) in 71-90% yields. Then, a series of substituted 2-aminopyridines were investigated under the reaction conditions. In general, electron-donating methyl derivatives of 2-aminopyridine were well-tolerated, delivering the desired products (**3f**–**3h**) in 84–91% yields. However, 2,2,2-trifluoro-*N*-(6-methylpyridin-2-yl)acetamide, gave the desired product **3i** in 24% yield, while 66% yield of amide bond insertion product **3i'** was observed.[6] We speculated that it was probably due to the unfavorable steric interaction between the methyl group and incoming benzyne. 2-Aminopyridine with a weak electron-withdrawing bromo group at 5-position furnished the desired product **3j** in moderate yield (61%), as it could readily undergo deacylation under the reaction conditions. Changing R^1 to benzoyl group rendered the product **3k** in a slightly higher yield of 69%. In addition, 1-aminoisoquinoline derivative and 2-benzoxazolinone were also compatible substrates, affording **3l** and **3n** in 84 and 72% yields, respectively. Similar to **3i**, 44% yield of **3m** was obtained along with 25% yield of insertion product **3m'** due to the steric hindrance. Furthermore, a variety of *o*-(trimethylsilyl)aryl triflates (**1b**–**1e**) were examined, furnishing the expected products (**3o**–**3r**) in satisfactory yields. Of note, 3-methoxyl aryne precursor **1c** afforded **3p** as a single regioisomer due to the steric and electronic effects. The regiochemistry of **3p** was confirmed with high-resolution ^{1}H-NMR and NOE experiments (see SI). Finally, it should be pointed out that the reaction of **3a** could be scaled up to 4 mmol, 88% of yield could be obtained, without obvious deterioration in the yield and selectivity.

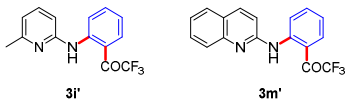
Table 2. Scope of *N*-Arylation Reaction[a,b]







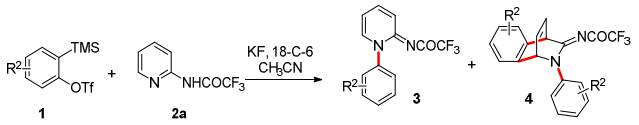
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.9 mmol), KF (1.0 mmol), 18-Crown-6 (1.0 mmol), CH_3CN (5 mL), rt (25 °C), air. [b]Isolated yield. [c]**3i'** was obtained in 66% yield along with **3i**. [d]**3m'** was obtained in 25% yield along with **3m**. [e]The reaction was conducted in 4 mmol scale.



3i' 3m'

While optimizing the reaction conditions, it was observed that increasing the amounts of **1a** and 18-Crown-6 at lower concentration, **4a** could be isolated as the major product in 61% yield along with 32% yield of **3a** (Table 3, entry 1). Increasing the reaction temperature to 50 °C led to lower yield of **4a** (entry 2). The best result was obtained when 5.0 equiv of **1a** was used with respect to **2a**, in the presence of 5.0 equiv of KF/18-Crown-6 in CH_3CN (0.01 M) at rt and the yield of **4a** was enhanced to 85% (entry 4). Unfortunately, electron-withdrawing substrate **1b** failed to undergo this transformation. Of particular note, even **3o** was not observed under the reaction conditions (entry 5). In order to further understand the results, previously synthesized dihydropyridines **3a**, **3b**, or **3o** (see Table 2) were used as diene substrates to react with **1b**, however Diels-Alder products were still not observed. In addition, 3-methoxybenzyne precursor **1c** was also found to be inapplicable substrate, as **4c** was not observed (entry 6). However, aryne precursor **1e** with weak electron-donating substituents proceeded smoothly to furnish benzoisoquinuclidine **4b** in 68% yield (entry 7).

Table 3. Optimization and Diels-Alder Reaction of Arynes with 2a[a]



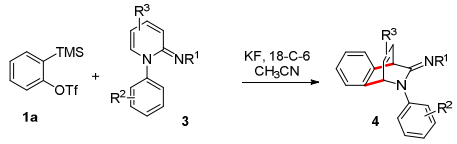
1 2a 3 4

entry	1	1:2a	KF/18-Crown-6 (equiv)	yield[b] (%)	
1	**1a**	3:1	3	**3a** (32)	**4a** (61)
2[c]	**1a**	3:1	3	**3a** (36)	**4a** (51)
3	**1a**	5:1	5	**3a** (0)	**4a** (82)
4[d]	**1a**	5:1	5	**3a** (0)	**4a** (85)
5[d]	**1b**	5:1	5	**3o** (0)	**4d** (0)
6[d]	**1c**	5:1	5	**3p** (trace)	**4c** (0)
7[d]	**1e**	5:1	5	**3r** (trace)	**4b** (68)

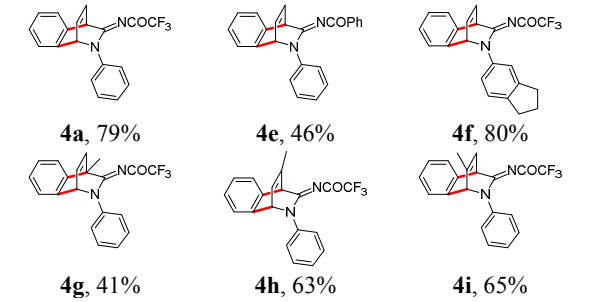
[a]Reaction conditions: **2a** (0.3 mmol, 0.025 M), **1**, KF/18-Crown-6, CH_3CN, rt, air. [b]Isolated yield. [c]50 °C was employed instead. [d]The concentration of **2a** (0.01 M) was applied instead.

We speculated that **4** probably was derived from **2** via *N*-arylation reaction followed by Diels-Alder reaction in a tandem manner. To demonstrate it, we allowed **1a** to react with a variety of 1-arylpyridin-2(1*H*)-imine derivatives, and all of them proceeded smoothly and afforded a library of diverse benzoisoquinuclidines (Table 4, **4a**–**4i**) in moderate to good yields, even with the substrate **3f** bearing a methyl group at the 3-position of 1-arylpyridin-2(1*H*)-imine to construct quaternary carbon center. It should be pointed out that trifluoroacetamide substrate **3a** exhibited better performance than that of benzamide **3d**, R^2 had little effects on the transformation (e.g., **3r**), and substituent R^3 of dienes (**3f**–**3h**) strongly influenced the efficiency of Diels-Alder reaction, resulting in considerable amounts of starting material of **3** retained when excessive benzyne had depleted.

Table 4. Diels-Alder Reaction of 1a with 3[a]



1a 3 4

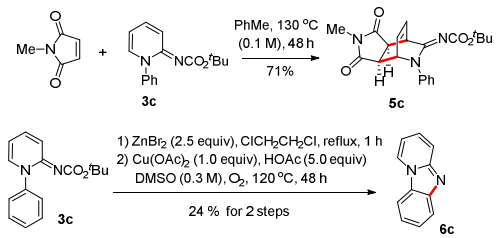


[a]Reaction conditions: **3** (0.2 mmol, 0.01 M), **1a** (2.5 equiv), KF/18-Crown-6 (2.5 equiv), CH_3CN, rt, air. Isolated yield.

To further explore the utility of the products obtained via *N*-arylation reaction of 2-aminopyridine derivatives, we performed the Diels-Alder reaction of **3c** with an ordinary dienophile, such as *N*-methylsuccinimide, leading to the formation of **5c** in 71% yield under thermal conditions (Scheme 2). The

relative stereochemistry of **5c** was confirmed by NOE experiments and X-ray diffraction studies (see SI). Furthermore, we also tried the cyclization reaction of **3c** through deprotecting and modified copper mediated cyclization reaction,[9] and pyrido[1,2-*a*]benzimidazole (**6c**) was obtained in 24% yield over two steps without further optimization. It should be mentioned that this is the first case of (aryl) C-N (amidinyl) bond forming reaction as the key step to construct pyrido[1,2-*a*]benzimidazole, to the best of our knowledge.[10]

Scheme 2. Diels-Alder Reaction of 3c with *N*-Methylsuccinimide and Cyclization Reaction of 3c



CONCLUSIONS

In summary, a chemoselective *N*-arylation reaction of 2-aminopyridine derivatives and arynes generated *in situ* from *o*-(trimethylsilyl)aryl triflates has been developed and good to excellent yields were obtained. The products obtained from this transformation can be further applied to the facile construction of benzoisoquinuclidines via Diels-Alder reaction with arynes in one pot or stepwise and isoquinuclidines via a two-step protocol, where the second step involves the reaction with a dienophile. The useful transformation of an *N*-arylation product to pyrido[1,2-*a*]benzimidazole is also demonstrated.

EXPERIMENTAL SECTION

General Information. All isolated compounds were characterized on Varian 300, Bruker 400, JEOL 400, and Varian 600 MHz spectrometers in $CDCl_3$, DMSO-d_6 or $(CD_3)_2CO$. Chemical shifts were reported as δ values relative to internal $CHCl_3$ (δ 7.26 for ^{1}H NMR and 77.00 for ^{13}C NMR), DMSO (δ 2.50 for ^{1}H NMR and 39.52 for ^{13}C NMR), and $(CH_3)_2CO$ (δ 2.05 for ^{1}H NMR and 29.84 for ^{13}C NMR). ^{19}F NMR chemical shifts were determined as δ values relative to external standard $PhCF_3$ at -63.00. High-resolution mass spectra (HRMS) were obtained on a 4G mass spectrometer by using electrospray ionization (ESI) analyzed by quadrupole time-of-flight (QTof). All melting points were measured with the samples after column chromatography and uncorrected. Column chromatography was performed on silica gel. Anhydrous THF and toluene were distilled over sodium benzophenone ketyl under Ar. All other solvents and reagents were used as obtained from commercial sources without further purification.

General Procedure for the Syntheses of Acylated 2-Amino Pyridine Derivatives (2a–2m).

To a solution of 2-aminopyridine (1 mmol, 1.0 equiv) and triethylamine (1.5 equiv) in DCM (10 mL) at 0 °C was added acylation reagent such as trifluoroacetic anhydride or acyl chloride (1.5 equiv), which was then allowed to stir for 24 h at room temperature. The mixture was quenched with Sat. NH_4Cl and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to afford acylated 2-amino pyridine derivative. An additional deacylation step (conditions: NaOH/MeOH/dioxane) was used to get the desired substrate **2d** (*N*-(pyridin-2-yl)benzamide), because diacylated product was often obtained as the major product. **2a**–**2m** are all known except substrate **2l**, and for **2a**–**2e**, **2h**–**2k** there are data reported in literature. **2n** is commercially available.

General Procedure for the Syntheses of 3a–3r via *N*-Arylation of 2-Amino Pyridine Derivatives.

To a solution of *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**, 90 mg, 0.30 mmol), 2,2,2-trifluoro-*N*-(pyridin-2-yl)acetamide (**2a**, 103 mg, 0.540 mmol), and 18-Crown-6 (158 mg, 0.600 mmol) in CH_3CN (3 mL), KF (35 mg, 0.60 mmol) was added and the resulting solution was stirred at room temperature for 10 h. After removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (EA) to give **3a** (71 mg, 89%) as a yellow solid.

Scale-up Experiment: To a solution of *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**, 1.19 g, 4.00 mmol), 2,2,2-trifluoro-*N*-(pyridin-2-yl)acetamide (**2a**, 1.37 g, 7.20 mmol), and 18-Crown-6 (2.11 g, 8.00 mmol) in CH_3CN (40 mL), KF (465 mg, 8.00 mmol) was added and the resulting solution was stirred at room temperature for 10 h. After removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (EA) to give **3a** (941 mg, 88%) as a yellow solid.

Other *N*-arylation reactions of acylated 2-amino pyridine derivatives **2** were conducted following a similar method. Reaction conditions: **1** (0.5 mmol), **2** (0.9 mmol, 1.8 equiv), KF (1.0 mmol, 2.0 equiv), 18-Crown-6 (1.0 mmol, 2.0 equiv), CH_3CN (5 mL), rt, air, 10–24 h.

General Procedure for Diels-Alder Reaction of 2a and Aryne.

To a solution of 2,2,2-trifluoro-*N*-(pyridin-2-yl)acetamide (**2a**, 57 mg, 0.30 mmol), *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**, 447 mg, 1.50 mmol), and 18-Crown-6 (396 mg, 1.50 mmol) in CH_3CN (30 mL), KF (87 mg, 1.5 mmol) was added and the mixture was stirred at room temperature for 24 h. After removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (PE:EA = 15:1) to give **4a** (88 mg, 85%) as a yellow oil.

Other Diels-Alder reactions of **2a** and aryne were conducted following a similar method. Reaction conditions: **2a** (0.3 mmol), **1** (1.5 mmol, 5 equiv), KF (1.5 mmol, 5 equiv), 18-Crown-6 (1.5 mmol, 5 equiv), CH_3CN (30 mL), rt, air, 24 h.

General Procedure for Diels-Alder Reaction of 3 with 1a.

To a solution of 2,2,2-trifluoro-*N*-(1-phenylpyridin-2(1*H*)-ylidene)acetamide (**3a**, 53 mg, 0.20 mmol), *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1a**, 149 mg, 0.500 mmol), and 18-Crown-6 (132 mg, 0.500 mmol) in CH_3CN (20 mL), KF (29 mg, 0.50 mmol) was added and the mixture was stirred at room temperature for 24 h. After removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (PE:EA = 15:1) to give **4a** (53 mg, 79%) as a yellow oil.

Other Diels-Alder reactions of **3** with **1a** were conducted following a similar method. Reaction conditions: **3** (0.2 mmol), **1a** (0.5 mmol, 2.5 equiv), KF (0.5 mmol, 2.5 equiv), 18-Crown-6 (0.5 mmol, 2.5 equiv), CH_3CN (20 mL), rt, air, 24 h.

Procedure for Diels-Alder reaction of *N*-Methylsuccinimide and 3c.

To a mixture of **3c** (27 mg, 0.10 mmol) and *N*-methylsuccinimide (33 mg, 0.30 mmol, 3.0 equiv) was added toluene (1 mL) under Ar, the resulting solution was heated at 130 ^{o}C for 48 h. After cooling and removing the solvent under reduced pressure, the resulting residue was purified by flash chromatography (PE:EA = 15:1) to give **5c** (27 mg, 71%) as a white solid.

Procedure for Cyclization Reaction of 3c.

To a solution of (**3c**, 86 mg, 0.32 mmol) in DCE (3.2 mL), $ZnBr_2$ (179 mg, 0.795 mmol, 2.5 equiv) was added and the mixture was stirred at 80 ^{o}C for 1 h. After cooling, the solution was diluted with EA (50 mL), quenched with Sat. Na_2CO_3 (10 drops), and stirred for additional 20 min. The resulting mixture was directly dried over Na_2SO_4, filtered, concentrated to give the crude 1-phenylpyridin-2(1*H*)-imine, which was used for the next step without further purification for its high polarity.

To a solution of above-mentioned 1-phenylpyridin-2(1*H*)-imine and $Cu(OAc)_2$ (58 mg, 0.32 mmol, 1.0 equiv) in DMSO (1 mL), HOAc (96 mg, 1.6 mmol, 5.0 equiv) was added. Then the mixture was evacuated, backfilled with O_2, and heated at 120 ^{o}C for 48 h. After finishing, the solution was cooled, diluted with Et_2O, and added with Sat. Na_2CO_3. Then the mixture was filtered through a short plug of celite. The organic layer was separated and washed with Sat. NaCl twice. Next, the organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (PE:EA:TEA = 1:1:1%) to give **6c** (13 mg, 24%, 2 steps) as a yellow solid.

Characterization Data of Substrates 2a–2m.

2,2,2-Trifluoro-N-(pyridin-2-yl)acetamide **2a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (br s, 1H), 8.35 (dd, J = 4.8, 0.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.86–7.77 (m, 1H), 7.19 (ddd, J = 7.2, 4.8, 0.4 Hz, 1H). ^{1}H NMR data correspond to the reported values.[11]

Methyl pyridin-2-ylcarbamate **2b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (br s, 1H), 8.34 (d, J = 4.2 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.05–6.95 (m, 1H), 3.83 (s, 3H). ^{1}H NMR data correspond to the reported values.[12]

tert-Butyl pyridin-2-ylcarbamate **2c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 8.33–8.28 (m, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.66 (td, J = 7.8, 2.0 Hz, 1H), 6.94 (dd, J = 7.2, 5.2 Hz, 1H), 1.54 (s, 9H). ^{1}H NMR data correspond to the reported values.[13]

N-(Pyridin-2-yl)benzamide **2d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.22 (dq, J = 5.2, 0.8 Hz, 1H), 7.95–7.90 (m, 2H), 7.75 (td, J = 7.8, 2.0 Hz, 1H), 7.56 (tt, J = 7.2, 2.0 Hz, 1H), 7.52–7.46 (m, 2H), 7.05 (ddd, J = 7.2, 4.8, 0.8 Hz, 1H). ^{1}H NMR data correspond to the reported values.[14]

N-(Pyridin-2-yl)pivalamide **2e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30–8.21 (m, 2H), 8.03 (br s, 1H), 7.74–7.66 (m, 1H), 7.07–7.00 (m, 1H), 1.33 (s, 9H). ^{1}H NMR data correspond to the reported values.[15]

2,2,2-Trifluoro-N-(3-methylpyridin-2-yl)acetamide **2f**. Compound **2f** was isolated as a white solid; mp 104–105 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.22–7.14 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (q, J = 36.9 Hz), 150.2, 141.4, 141.3, 131.0, 121.2, 116.3 (q, J = 285.8 Hz), 17.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.54 (s, 3F); ESI-HRMS *m/z* calcd for $C_8H_8F_3N_2O$ $[M+H]^+$ 205.0583, found 205.0583.

2,2,2-Trifluoro-N-(4-methylpyridin-2-yl)acetamide **2g**. Compound **2g** was isolated as a white solid; mp 76–77 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (br s, 1H), 8.17 (d, J = 4.8 Hz, 1H), 8.04–7.99 (m, 1H), 7.00 (d, J = 4.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (q, J = 37.9 Hz), 150.9, 149.6, 147.3, 122.6, 116.0, 115.7 (q, J = 339.7 Hz), 21.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.70 (s, 3F); ESI-HRMS *m/z* calcd for $C_8H_8F_3N_2O$ $[M+H]^+$ 205.0583, found 205.0584.

2,2,2-Trifluoro-N-(5-methylpyridin-2-yl)acetamide **2h**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 8.18–8.14 (m, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.64–7.58 (m, 1H), 2.34 (s, 3H). ^{1}H NMR data correspond to the reported values.[16]

2,2,2-Trifluoro-N-(6-methylpyridin-2-yl)acetamide **2i**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (br s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70–7.63 (m, 1H), 7.02 (d, J = 7.5 Hz, 1H), 2.46 (s, 3H). ^{1}H NMR data correspond to the reported values.[17]

N-(5-Bromopyridin-2-yl)-2,2,2-trifluoroacetamide **2j**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.41 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 8.7, 0.6 Hz, 1H), 7.91 (dd, J = 8.7, 2.7 Hz, 1H). ^{1}H NMR data correspond to the reported values.[18]

N-(5-Bromopyridin-2-yl)benzamide **2k**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 8.36–8.32 (m, 2H), 7.93–7.89 (m, 2H), 7.86 (dd, J = 8.8, 2.4 Hz, 1H), 7.62–7.56 (m, 1H), 7.51 (t, J = 7.6 Hz, 2H). ^{1}H NMR data correspond to the reported values.[19]

2,2,2-Trifluoro-N-(quinolin-2-yl)acetamide **2l**. Compound **2l** was isolated as as a white solid; mp 95–96 ^{o}C. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 14.47 (br s, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.4 Hz, 1H), 8.00–7.93 (m, 2H), 7.85–7.73 (m, 1H), 7.56 (d, J = 6.8 Hz, 1H); ^{13}C NMR (150 MHz, CD_3COCD_3) δ C (*C=O*, due to the poor solubility of **2l**, peak of *C=O* is obscure), 138.8, 135.2, 129.4, 128.4, 128.3, 128.0, 127.8, 125.8, 118.1 (q, J = 285.0 Hz), 115.9; ^{19}F NMR (282 MHz, CD_3COCD_3) δ -76.13 (s, 3F); ESI-HRMS *m/z* calcd for $C_{11}H_8F_3N_2O$ $[M+H]^+$ 241.0583, found 241.0580.

2,2,2-Trifluoro-N-(isoquinolin-1-yl)acetamide **2m**. Compound **2m** was isolated as a white solid; mp 235–237 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.74 (td, J = 8.4, 1.5 Hz, 1H), 7.60–7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3 (q, J = 38.2 Hz), 150.0, 144.7, 139.7, 130.7, 127.7, 126.4, 126.3, 115.7 (q, J = 286.5 Hz), 115.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.23 (s, 3F); ESI-HRMS *m/z* calcd for $C_{11}H_8F_3N_2O$ $[M+H]^+$ 241.0583, found 241.0583.

Characterization Data of Products (3a–3r, 3i', 3m' 4a–4i, 5c, and 6c).

2,2,2-Trifluoro-N-(1-phenylpyridin-2(1H)-ylidene)acetamide.

Compound **3a** (71 mg, Y = 89%, R_f = 0.6 (EA)) was isolated as a yellow solid; mp 98–99 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 1H), 7.87–7.79 (m, 1H), 7.77 (dd, J = 6.8, 1.2 Hz, 1H), 7.51–7.41 (m, 3H), 7.35–7.27 (m, 2H), 6.90 (td, J = 6.8, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (q, J = 34.5 Hz), 160.1, 142.2, 141.3, 139.6, 129.4, 129.1, 126.1, 122.1, 117.0 (q, J = 286.3 Hz), 114.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.48 (s, 3F); ESI-HRMS *m/z* calcd for $C_{13}H_{10}F_3N_2O$ $[M+H]^+$ 267.0740, found 267.0737.

Methyl (1-phenylpyridin-2(1H)-ylidene)carbamate. Compound **3b** (86 mg, Y = 75%, R_f = 0.2 (EA)) was isolated as a yellow solid; mp 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 9.2 Hz, 1H), 7.54–7.37 (m, 5H), 7.35–7.27 (m, 2H), 6.46 (td, J = 6.8, 1.2 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 160.3, 142.0, 139.0, 138.4, 129.2, 128.6, 126.3, 119.9, 109.0, 52.0; ESI-HRMS *m/z* calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.0972, found 229.0970.

tert-Butyl (1-phenylpyridin-2(1H)-ylidene)carbamate. Compound **3c** (96 mg, Y = 71%, R_f = 0.2 (EA)) was isolated as a yellow solid; mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 9.6 Hz, 1H), 7.46–7.40 (m, 2H), 7.39–7.33 (m, 2H), 7.30 (d, J = 7.2 Hz, 3H), 6.31 (td, J = 6.8, 0.8 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 159.5, 142.2, 138.3, 138.2, 129.1, 128.4, 126.6, 120.1, 108.1, 78.1, 28.2; ESI-HRMS *m/z* calcd for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ 271.1441, found 271.1443.

N-(1-Phenylpyridin-2(1H)-ylidene)benzamide. Compound **3d** (124 mg, Y = 90%, R_f = 0.4 (EA)) was isolated as a yellow solid; mp 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 9.2 Hz, 1H), 7.96–7.87 (m, 2H), 7.57–7.40 (m, 5H), 7.39–7.28 (m, 3H), 7.23 (t, J = 7.4 Hz, 2H), 6.49 (td, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 159.2, 142.2, 139.7, 138.7, 138.5, 130.5, 129.0, 128.9, 128.6, 127.4, 126.5, 121.2, 110.3; ESI-HRMS *m/z* calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$ 275.1179, found 275.1175.

N-(1-Phenylpyridin-2(1H)-ylidene)pivalamide. Compound **3e** (102 mg, Y = 80%, R_f = 0.2 (EA)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 9.2 Hz, 1H), 7.50–7.38 (m, 5H), 7.35–7.28 (m, 2H), 6.43 (td, J = 6.8, 1.2 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 158.5, 142.3, 139.0, 138.1, 128.7, 128.3, 126.6, 120.7, 109.0, 41.1, 27.6; ESI-HRMS *m/z* calcd for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492, found 255.1498.

2,2,2-Trifluoro-N-(3-methyl-1-phenylpyridin-2(1H)-ylidene)acetamide. Compound **3f** (127 mg, Y = 91%, R_f = 0.2 (EA)) was isolated as a yellow solid; mp 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 16.0, 7.2 Hz, 2H), 7.50–7.38 (m, 3H), 7.36–7.27 (m, 2H), 7.05 (t, J = 6.8 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 157.0 (q, J = 34.5 Hz), 143.0, 141.0, 137.8, 133.4, 129.8, 129.4, 129.2, 125.0, 117.3 (q, J = 285.3 Hz), 116.1, 18.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.55 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$ 281.0896, found 281.0894.

2,2,2-Trifluoro-N-(4-methyl-1-phenylpyridin-2(1H)-ylidene)acetamide. Compound **3g** (119 mg, Y = 85%, R_f = 0.6 (EA)) was isolated as a yellow solid; mp 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.67 (d, J = 6.8 Hz, 1H), 7.51–7.41 (m, 3H), 7.35–7.26 (m, 2H), 6.77 (dd, J = 6.8, 1.6 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (q, J = 34.3 Hz), 159.3, 155.4, 141.0, 138.7, 129.2, 129.0, 126.1, 121.2, 117.1 (q, J = 286.3 Hz), 116.3, 21.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.75 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$ 281.0896, found 281.0894.

2,2,2-Trifluoro-N-(5-methyl-1-phenylpyridin-2(1H)-ylidene)acetamide. Compound **3h** (118 mg, Y = 84%, R_f = 0.7 (EA)) was isolated as a yellow solid; mp 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 9.2, 2.4 Hz, 1H), 7.61 (s, 1H), 7.51–7.42 (m, 3H), 7.35–7.27 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (q, J = 34.4 Hz), 158.4, 144.3, 141.3, 137.8, 129.2, 129.0, 126.0, 124.6, 121.6, 117.1 (q, J = 286.2 Hz), 17.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.28 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$ 281.0896, found 281.0894.

2,2,2-Trifluoro-N-(6-methyl-1-phenylpyridin-2(1H)-ylidene)acetamide. Compound **3i** (34 mg, Y = 24%, R_f = 0.5 (EA)) was isolated as a white solid; mp 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 9.2 Hz, 1H), 7.75 (dd, J = 8.8, 7.6 Hz, 1H), 7.58–7.43 (m, 3H), 7.16–7.10 (m, 2H), 6.81 (d, J = 7.2 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (q, J = 35.1 Hz), 161.6, 149.0, 142.0, 139.0, 129.6, 129.2, 126.2, 119.1, 117.0 (q, J = 286.4 Hz), 115.2, 22.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.23 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$ 281.0896, found 281.0895.

N-(5-Bromo-1-phenylpyridin-2(1H)-ylidene)-2,2,2-trifluoroacetamide. Compound **3j** (105 mg, Y = 61%, R_f = 0.5 (PE:EA = 2:1)) was isolated as a yellow solid; mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 9.6 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 9.3, 2.4 Hz, 1H), 7.56–7.46 (m, 3H), 7.39–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 (q, J = 35.0 Hz), 159.0, 144.6, 140.7, 139.4, 129.8, 129.3, 126.0, 122.8, 116.8 (q, J = 286.0 Hz), 106.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.85 (s, 3F); ESI-HRMS *m/z* calcd for $C_{13}H_9BrF_3N_2O$ $[M+H]^+$ 344.9845, found 344.9844.

N-(5-Bromo-1-phenylpyridin-2(1H)-ylidene)benzamide. Compound **3k** (123 mg, Y = 69%, R_f = 0.4 (PE:EA = 2:1)) was isolated as a yellow solid; mp 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 10.0 Hz, 1H), 7.93–7.85 (m, 2H), 7.66 (d, J = 2.0 Hz, 1H), 7.60–7.43 (m, 4H), 7.43–7.30 (m, 3H), 7.24 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 157.6, 142.2, 141.5, 138.2, 130.9, 129.1, 129.0, 127.5, 126.5, 122.0, 102.1, (2C missing); ESI-HRMS *m/z* calcd for $C_{18}H_{14}BrN_2O$ $[M+H]^+$ 353.0284, found 353.0285.

2,2,2-Trifluoro-N-(2-phenylisoquinolin-1(2H)-ylidene)acetamide. Compound **3l** (132 mg, Y = 84%, R_f = 0.5 (EA)) was isolated as a white solid; mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.4 Hz, 1H), 7.90–7.81 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.73–7.64 (m, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.53–7.39 (m, 5H), 7.30 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 157.8 (q, J = 35.4 Hz), 141.6, 136.7, 134.7, 132.3, 129.6, 129.5, 129.4, 129.4, 126.9, 125.4, 124.1, 117.2 (q, J = 285.6 Hz), 115.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.08 (s, 3F); ESI-HRMS *m/z* calcd for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$ 317.0896, found 317.0894.

2,2,2-Trifluoro-N-(1-phenylquinolin-2(1H)-ylidene)acetamide. Compound **3m** (69 mg, Y = 44%, R_f = 0.4 (PE:EA = 2:1)) was isolated as a yellow solid; mp 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 9.6 Hz, 1H), 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.65–7.49 (m, 4H), 7.48–7.41 (m, 1H), 7.28–7.20 (m, 2H), 6.93 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (q, J = 35.3 Hz), 161.0, 141.2, 139.7, 137.9, 131.9, 129.9, 129.4, 128.6, 127.7, 125.1, 122.9, 119.2, 118.1, 116.8 (q, J = 286.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.11 (s, 3F); ESI-HRMS *m/z* calcd for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$ 317.0896, found 317.0892.

4-Phenyloxazolo[4,5-b]pyridin-2(4H)-one. Compound **3n** (76 mg, Y = 72%, R_f = 0.5 (EA)) was isolated as a white solid; mp 212–

213 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.92 (dd, J = 6.9, 0.9 Hz, 1H), 6.82–6.54 (m, 6H), 6.04 (t, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.5, 159.5, 144.0, 139.3, 131.1, 129.8, 129.6, 125.7, 112.5, 112.4; ESI-HRMS *m/z* calcd for $C_{12}H_9N_2O_2$ $[M+H]^+$ 213.0659, found 213.0656.

N-(1-(3,4-Difluorophenyl)pyridin-2(1H)-ylidene)-2,2,2-trifluoroacetamide. Compound **3o** (88 mg, Y = 58%, R_f = 0.5 (EA)) was isolated as a yellow solid; mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 9.2 Hz, 1H), 7.91–7.84 (m, 1H), 7.80–7.74 (m, 1H), 7.37–7.24 (m, 2H), 7.17–7.08 (m, 1H), 6.94 (td, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (q, J = 34.9 Hz), 160.2, 151.5 (dd, J = 84.2, 10.7 Hz), 149.1 (dd, J = 79.3, 10.8 Hz), 142.6, 139.2, 137.1 (dd, J = 7.9, 3.9 Hz), 122.9 (dd, J = 6.8, 4.0 Hz), 122.1, 117.8 (dd, J = 18.7, 0.8 Hz), 116.9 (q, J = 286.2 Hz), 116.6 (dd, J = 20.1, 1.0 Hz), 114.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.58 (s, 3F), -134.11 (m, 1F), -134.62 (m 1F); ESI-HRMS *m/z* calcd for $C_{13}H_8F_5N_2O$ $[M+H]^+$ 303.0551, found 303.0549.

2,2,2-Trifluoro-N-(1-(3-methoxyphenyl)pyridin-2(1H)-ylidene)acetamide. Compound **3p** (111 mg, Y = 75%, R_f = 0.6 (EA)) was isolated as a yellow solid; mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 8.8 Hz, 1H), 7.88–7.73 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 6.98 (dd, J = 8.0, 1.2 Hz, 1H), 6.93–6.80 (m, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (q, J = 34.5 Hz), 160.0, 159.8, 142.2, 142.1, 139.6, 129.8, 122.1, 118.1, 117.0 (q, J = 286.3 Hz), 115.5, 114.1, 112.0, 55.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.40 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{12}F_3N_2O_2$ $[M+H]^+$ 297.0845, found 297.0843.

N-(1-(Benzo[d][1,3]dioxol-5-yl)pyridin-2(1H)-ylidene)-2,2,2-trifluoroacetamide. Compound **3q** (121 mg, Y = 78%, R_f = 0.5 (EA)) was isolated as a yellow solid; mp 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 6.6 Hz, 1H), 6.98–6.80 (m, 3H), 6.75 (dd, J = 8.1, 1.8 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (q, J = 34.6 Hz), 160.3, 148.3, 147.9, 142.0, 139.9, 135.0, 122.0, 119.5, 117.0 (q, J = 286.3 Hz), 114.0, 108.0, 107.5, 102.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.72 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{10}F_3N_2O_3$ $[M+H]^+$ 311.0638, found 311.0637.

N-(1-(2,3-Dihydro-1H-inden-5-yl)pyridin-2(1H)-ylidene)-2,2,2-trifluoroacetamide. Compound **3r** (118 mg, Y = 77%, R_f = 0.5 (EA)) was isolated as a yellow solid; mp 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.8 Hz, 1H), 7.89–7.72 (m, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 6.4 Hz, 1H), 3.01–2.88 (m, 4H), 2.20–2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (q, J = 34.5 Hz), 160.2, 145.6, 145.4, 141.8, 140.0, 139.4, 124.5, 123.8, 122.1, 121.9, 117.1 (q, J = 286.3 Hz), 114.1, 32.6, 32.4, 25.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.24 (s, 3F); ESI-HRMS *m/z* calcd for $C_{16}H_{14}F_3N_2O$ $[M+H]^+$ 307.1053, found 307.1052.

2,2,2-Trifluoro-1-(2-((6-methylpyridin-2-yl)amino)phenyl)ethan-1-one. Compound **3i'** (92 mg, Y = 66%, R_f = 0.6 (PE:EA = 5:1)) was isolated as an orange-yellow solid; mp 59–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.83 (d, J = 8.8 Hz, 1H), 7.94–7.85 (m, 1H), 7.63–7.56 (m, 1H), 7.52 (t, J = 7.8 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7 (q, J = 33.3 Hz), 157.1, 153.2, 147.8, 138.0, 137.1, 131.7 (q, J = 4.0 Hz), 118.7, 118.2, 117.0 (q, J = 289.5 Hz), 117.0, 113.1, 110.8, 24.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.81 (s, 3F); ESI-HRMS *m/z* calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$ 281.0896, found 281.0894.

2,2,2-Trifluoro-1-(2-(quinolin-2-ylamino)phenyl)ethan-1-one. Compound **3m'** (40 mg, Y = 25%, R_f = 0.5 (PE:EA = 5:1)) was isolated as an orange-yellow solid; mp 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 9.52 (d, J = 8.4 Hz, 1H), 8.05–7.87 (m, 3H), 7.77–7.59 (m, 3H), 7.45–7.33 (m, 1H), 7.06–7.00 (m, 1H), 6.97 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2 (q, J = 33.5 Hz), 152.4, 147.0, 146.9, 137.8, 137.4, 131.8 (q, J = 4.1 Hz), 129.8, 127.6, 127.4, 124.7, 124.4, 119.6, 119.6, 117.0 (q, J = 289.5 Hz), 115.1, 113.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -69.14 (s, 3F); ESI-HRMS *m/z* calcd for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$ 317.0896, found 317.0894.

Compound **4a** (88 mg, Y = 85%, R_f = 0.2 (PE:EA = 5:1)) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.48 (m, 1H), 7.38–7.29 (m, 3H), 7.28–7.20 (m, 1H), 7.21–7.12 (m, 4H), 7.11–7.03 (m, 2H), 6.01 (dd, J = 5.6, 2.4 Hz, 1H), 5.79 (dd, J = 4.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 165.9 (q, J = 35.8 Hz), 140.9, 139.6, 139.0, 137.0, 136.9, 129.0, 127.6, 126.8, 126.3, 125.0, 124.0, 122.2, 116.6 (q, J = 286.1 Hz), 66.1, 50.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.13 (s, 3F); ESI-HRMS *m/z* calcd for $C_{19}H_{14}F_3N_2O$ $[M+H]^+$ 343.1053, found 343.1051.

Compound **4b** (87 mg, Y = 68%, R_f = 0.4 (PE:EA = 5:1)) was isolated as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.24–7.18 (m, 2H), 7.14–7.07 (m, 2H), 7.03 (d, J = 1.8 Hz, 1H), 6.94 (dd, J = 7.8, 1.8 Hz, 1H), 5.93 (dd, J = 5.4, 1.8 Hz, 1H), 5.70 (dd, J = 5.4, 1.8 Hz, 1H), 2.95–2.84 (m, 8H), 2.13–2.06 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 165.9 (q, J = 35.7 Hz), 145.3, 144.0, 143.0, 142.3, 139.6, 138.0, 137.6, 137.4, 137.2, 124.6, 122.1, 121.5, 120.1, 118.6, 116.7 (q, J = 286.0 Hz), 67.0, 50.2, 32.8, 32.5, 32.5, 25.6, 25.5, (1C missing); ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.05 (s, 3F); ESI-HRMS *m/z* calcd for $C_{25}H_{22}F_3N_2O$ $[M+H]^+$ 423.1679, found 423.1678.

Compound **4e** (32 mg, Y = 46%, R_f = 0.5 (PE:EA = 3:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.96 (m, 2H), 7.46–7.26 (m, 9H), 7.23–7.18 (m, 1H), 7.16–7.10 (m, 2H), 7.07–7.01 (m, 2H), 5.90 (dd, J = 5.2, 2.8 Hz, 1H), 5.68 (dd, J = 4.4, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 164.6, 141.7, 141.2, 140.0, 137.1, 136.8, 131.7, 129.6, 128.7, 127.8, 126.4, 126.3, 126.0, 124.7, 124.3, 121.8, 64.5, 49.6, (1C missing); ESI-HRMS *m/z* calcd for $C_{24}H_{19}N_2O$ $[M+H]^+$ 351.1492, found 351.1493.

Compound **4f** (61 mg, Y = 80%, R_f = 0.5 (PE:EA = 3:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.72 (m, 1H), 7.38–7.33 (m, 1H), 7.24–7.15 (m, 3H), 7.12 (t, J = 3.6 Hz, 2H), 7.02 (s, 1H), 6.93 (dd, J = 8.0, 1.2 Hz, 1H), 6.02 (t, J = 3.4 Hz, 1H), 5.77 (t, J = 3.4 Hz, 1H), 2.90 (t, J = 7.6 Hz, 4H), 2.09 (quint, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 166.0 (q, J = 35.9 Hz), 145.4, 144.2, 141.0, 139.2, 137.9, 137.1, 136.9, 126.8, 126.3, 125.1, 124.7, 122.2, 122.1, 122.0, 116.6 (q, J = 286.0 Hz), 66.7, 50.2, 32.8, 32.5, 25.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.96 (s, 3F); ESI-HRMS *m/z* calcd for $C_{22}H_{18}F_3N_2O$ $[M+H]^+$ 383.1366, found 383.1367.

Compound **4g** (29 mg, Y = 41%, R_f = 0.25 (PE:EA = 3:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.34–7.28 (m, 2H), 7.28–

7.22 (m, 1H), 7.22–7.17 (m, 1H), 7.11 (dd, J = 6.8, 5.6 Hz, 1H), 7.04–6.96 (m, 2H), 6.76 (dd, J = 6.8, 1.6 Hz, 1H), 5.57 (dd, J = 5.6, 1.6 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 160.4 (q, J = 36.4 Hz), 142.6, 142.0, 141.3, 141.0, 136.8, 129.8, 128.3, 126.7, 126.2, 124.1, 122.6, 122.1, 116.3 (q, J = 286.5 Hz), 66.9, 55.1, 14.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.49 (s, 3F); ESI-HRMS *m/z* calcd for $C_{20}H_{16}F_3N_2O$ $[M+H]^+$ 357.1209, found 357.1212.

Compound **4h** (45 mg, Y = 63%, R_f = 0.5 (PE:EA = 3:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.48 (m, 1H), 7.41–7.36 (m, 2H), 7.35–7.28 (m, 1H), 7.31–7.26 (m, 1H), 7.24–7.15 (m, 4H), 6.63 (dt, J = 5.6, 2.0 Hz, 1H), 5.74–5.66 (m, 2H), 2.11 (d, J = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.0 (q, J = 35.9 Hz), 148.6, 141.5, 139.7, 139.1, 129.3, 129.0, 127.6, 126.6, 126.5, 124.8, 124.0, 121.6, 113.8 (d, J = 285.9 Hz), 66.6, 55.4, 18.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.15 (s, 3F); ESI-HRMS *m/z* calcd for $C_{20}H_{16}F_3N_2O$ $[M+H]^+$ 357.1209, found 357.1214.

Compound **4i** (46 mg, Y = 65%, R_f = 0.5 (PE:EA = 3:1)) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 6.4 Hz, 1H), 7.40–7.34 (m, 3H), 7.30–7.25 (m, 1H), 7.23–7.14 (m, 4H), 6.60 (dt, J = 6.0, 1.8 Hz, 1H), 5.86 (d, J = 6.0 Hz, 1H), 5.45 (d, J = 1.6 Hz, 1H), 2.06 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 166.0 (q, J = 35.9 Hz), 147.3, 140.8, 139.8, 139.7, 129.1, 128.9, 127.7, 127.1, 126.2, 124.8, 124.4, 122.1, 116.6 (q, J = 285.9 Hz), 70.9, 49.6, 18.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.06 (s, 3F); ESI-HRMS *m/z* calcd for $C_{20}H_{16}F_3N_2O$ $[M+H]^+$ 357.1209, found 357.1212.

Compound **5c** (27 mg, Y = 71%, R_f = 0.3 (PE:EA = 2:1)) was isolated as a white solid; mp 164–165 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.33 (m, 2H), 7.30–7.20 (m, 3H), 6.65–6.57 (m, 1H), 6.52–6.44 (m, 1H), 5.10–5.00 (m, 1H), 4.88–4.78 (m, 1H), 3.64 (dd, J = 8.1, 4.2 Hz, 1H), 3.45 (dd, J = 8.1, 3.3 Hz, 1H), 2.92 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 174.7, 162.2, 161.1, 140.5, 132.2, 131.7, 129.2, 126.9, 124.8, 80.5, 58.1, 46.7, 40.9, 40.6, 28.1, 25.0; ESI-HRMS *m/z* calcd for $C_{21}H_{24}N_3O_4$ $[M+H]^+$ 382.1761, found 382.1763.

Benzo[4,5]imidazo[1,2-a]pyridine. Compound **6c** (13 mg, Y = 24% for 2 steps, R_f = 0.1 (EA)) was isolated as a yellow solid; ^{1}H NMR (400 MHz, CD_3COCD_3) δ 8.91 (d, J = 6.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.58–7.47 (m, 2H), 7.40–7.33 (m, 1H), 6.97 (t, J = 6.8 Hz, 1H). ^{1}H NMR data correspond to the reported values.[20]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H, ^{13}C NMR, ^{19}F NMR, and 1D NOE spectra for substrates and all new compounds (PDF)

X-ray Crystallographic information for compound **5c** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: chengb@lzu.edu.cn.

*E-mail: zhaihb@pkusz.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank NSFC (21472072, 21302077, and 21290183), Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT_15R28), FRFCU (lzujbky-2016-ct02, lzujbky-2014-188) and "111" Program of MOE for financial support. We thank Dr. Hanwei Hu and Dr. Vaneet Saini for assistance in polishing the manuscript and Prof. Hai-Chao Xu for assistance in electrosynthetic attempt of pyrido[1,2-*a*]benzimidazole.

REFERENCES

(1) For pharmaceutical activities see: (a) Takeshita, H.; Watanabe, J.; Kimura, Y.; Kawakami, K.; Takahashi, H.; Takemura, M.; Kitamura, A.; Someya, K.; Nakajima, R. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3893. (b) Badaway, E.; Kappe, T. *Eur. J. Med. Chem.* **1995**, *30*, 327. (c) Kotovskaya, S. K.; Baskakova, Z. M.; Charushin, V. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Balakhnin, S. M.; Serova, O. A. *Pharm. Chem. J.* **2005**, *39*, 574. (d) Ndakala, A. J.; Gessner, R. K.; Gitari, P. W.; October, N.; White, K. L.; Hudson, A.; Fakorede, F.; Shackleford, D. M.; Kaiser, M.; Yeates, C.; Charman, S. A.; Chibale, K. *J. Med. Chem.* **2011**, *54*, 4581. (e) Koo, H. L.; Dupont, H. L. *Curr. Opin. Gastroenterol.* **2010**, *26*, 17. (f) Perin, N.; Uzelac, L.; Piantanida, I.; Karminski-Zamola, G.; Kralj, M.; Hranjec, M. *Bioorg. Med. Chem.* **2011**, *19*, 6329. For optical properties see: (g) Chalmers, B. A.; Saha, S.; Nguyen, T.; McMurtrie, J.; Sigurdsson, S. T.; Bottle, S. E.; Masters, K.-S. *Org. Lett.* **2014**, *16*, 5528. (h) Gong, W.; Gao, P.; Li, G.; Mehdi, H.; Ning, G.; Yu, J. *RSC Adv.* **2014**, *4*, 51268. (i) Yan, L.; Zhao, D.; Lan, J.; Cheng, Y.; Guo, Q.; Li, X.; Wu, N.; You, J. *Org. Biomol. Chem.* **2013**, *11*, 7966.

(2) (a) Kuzuya, M.; Mano, E.; Adachi, M.; Noguchi, A.; Okuda, T. *Chem. Lett.* **1982**, 475. (b) Kuzuya, M.; Noguchi, A.; Kamiya, S.; Okuda, T. *Chem. Pharm. Bull.* **1985**, *33*, 2313. (c) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Chem. Asian J.* **2010**, *5*, 153. (d) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454.

(3) (a) Mohareb, R. M.; Sherif, S. M.; Zohdi, H. F. *J. Chin. Chem. Soc.* (Taipei, Taiwan) **1993**, *40*, 181. (b) El-Sayed, A. M.; Abdel-Ghany, H. *J. Heterocyclic Chem.* **2000**, *37*, 1233. (c) Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1987**, *52*, 3289. (d) Ishii, M.; Mori, F.; Tanaka, K. *Chem. Eur. J.* **2014**, *20*, 2169. (e) Hachiya, I.; Minami, Y.; Aramaki, T.; Shimizu, M. *Eur. J. Org. Chem.* **2008**, 1411.

(4) For free amine see: (a) Rao, D. N.; Rasheed, S.; Aravinda, S.; Vishwakarma, R. A.; Das, P. *RSC Adv.* **2013**, *3*, 11472. (b) Kim, M.; Chang, S. *Org. Lett.* **2010**, *12*, 1640. (c) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481. For amide see: (d) Inukai, T.; Takeuchi, J.; Yasuhiro, T.; Wolf, M. A.; Pawal, V. D.; Chakrabarti, A.; Chittimalla, S. K. *PCT Int. Appl.* **2015**, WO 2015068767. (e)Taniguchi, T.; Yoshikawa, M.; Miura, K.; Hasui, T.; Honda, E.; Imamura, K.; Kamata, M.; Kamisaki, H.; Quinn, J. F.; Raker, J.; Camara, F.; Wang, Y. *PCT Int. Appl.* **2011**, WO 2011163355.

(5) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett*. **1983**, 1211.

(6) For some representative examples, see: (a) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198. (c) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (d) Haber, J. C.; Lynch, M. A.; Spring, S. L.; Pechulis, A. D.; Raker, J.; Wang, Y. *Tetrahedron Lett.* **2011**, *52*, 5847.

(7) Rayabarapu, D. K.; Majumdar, K. K.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66,* 3646.

(8) (a) Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2013**, *15*, 4620. (b) Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. *Angew. Chem., Int. Ed.* **2013**, *52*, 10040. (c) Rogness, D. C.; Markina, N. A.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 2743.

(9) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932.

(10) For some representative synthetic approaches see: (a) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2007**, 3155 and references therein. (b) Yan, C. G.; Wang, Q. F.; Song, X. K.; Sun, J. *J. Org. Chem.* **2009**, *74*, 710. (k) Xie, Y.; Wu, J.; Che, X.; Chen, Y.; Huang, H.; Deng, G.-J. *Green Chem.* **2016**, *18*, 667 and references therein.

(11) Mekhalfia, A.; Mutter, R.; Heal, W.; Chen, B. *Tetrahedron* **2006**, *62*, 5617.

(12) Shinomoto, Y.; Yoshimura, A.; Shimizu, H.; Yamazaki, M.; Zhdankin, V. V.; Saito, A. *Org. Lett.* **2015**, *17*, 5212.

(13) Varala, R.; Nuvula, S.; R. Adapa, S. R. *J. Org. Chem*. **2006**, *71*, 8283.

(14) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070.

(15) Katritzky, A. R.; El-Gendy, B. E.-D. M.; Todadze, E.; El-G.; Abdel-Fattah, A. A. A. *J. Org. Chem*. **2008**, *73*, 5442.

(16) Cho, Y. S.; Borland, M.; Brain, C.; Chen, C. H.-T.; Cheng, H.; Chopra, R.; Chung, K.; Groarke, J.; He, G.; Hou, Y.; Kim, S.; Kovats, S.; Lu, Y.; O'Reilly, M.; Shen, J.; Smith, T.; Trakshel, G.; Vögtle, M.; Xu, M.; Xu, M.; Sung, M. J. *J. Med. Chem.* **2010**, *53*, 7938.

(17) Shidlovskii, A. F.; Peregudov, A. S.; Averkiev, B. B.; Antipin, M. Y.; Chkanikov, N. D. *Russ. Chem. Bull., Int. Ed.* **2004**, *53,* 2060.

(18) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Heterocyclic Chem*. **1998**, *35*, 719.

(19) Ragupathi, A.; Sagadevan, A.; Lin, C.-C.; Hwu, J.-R.; Hwang, K. C. *Chem. Commun.* **2016**, *52*, 11756.

(20) Rao, D. N.; Rasheed, S.; Vishwakarm, R. A.; Das, P. *RSC Adv.* **2014**, *4*, 25600.