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Arylation, Alkenylation, and Alkylation of 2-Halopyridine *N*-Oxides with Grignard Reagents: A Solution to the Problem of C2/C6 Regioselective Functionalization of Pyridine Derivatives

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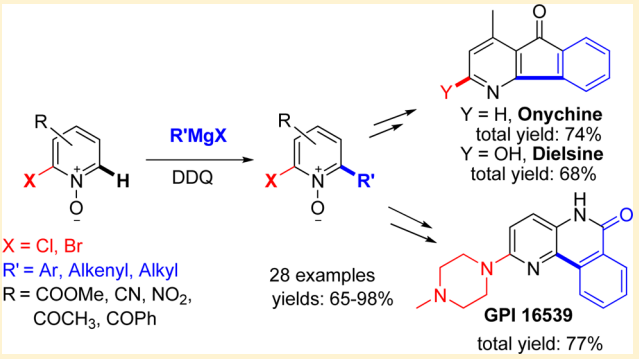
Supporting Information

ABSTRACT: A facile arylation, alkenylation, and alkylation of functionalized 2-halopyridine *N*-oxides with various Grignard reagents was developed. It represented a highly efficient and selective C−H bond functionalization of pyridine derivatives in the presence of reactive C−Cl or C−Br bonds. Using Cl or Br as a blocking group, C2/C6 site-controllable functionalization of pyridine derivatives has been achieved. Various pyridine compounds can be prepared as illustrated in the total syntheses of Onychine, dielsine, and PARP-1 inhibitor GPI 16539.



Pyridines are among the most widespread heterocyclic structural units in natural products, pharmaceuticals, biologically active compounds, and functional materials.[1] Pyridine *N*-oxides often serve as important intermediates for the activation and functionalization of pyridine by virtue of their high reactivity, ease of synthesis, and ready availability.[2] Numerous efforts have been devoted to developing efficient methods for the arylation, alkenylation, and alkylation of pyridine *N*-oxides. Among the reported methods, arylation or alkylation using Grignard reagents[3] and palladium-catalyzed direct arylation via C−H activation[4] represent the major strategies.[5] However, functionalization of 3-substituted pyridine *N*-oxides using these procedures would confront the problem of regiochemistry because of a competition between the two reactive positions C2 and C6,[6−8] and thus an efficient and general method to address this regioselectivity is highly desired. To this end, we herein report a simple transition-metal-free arylation, alkenylation, and alkylation of functionalized 2-halopyridine *N*-oxides. Since the halogen atom can block the otherwise competing reactive sites and can be subsequently removed, replaced, or used in a cross-coupling reaction, this one-pot procedure provides a practicable and general method for site-controllable functionalization of pyridine derivatives at C2 or C6.

Due to its high electrophilicity, 2-halopyridine *N*-oxide functions as one of key intermediates for the introduction of substituents at 2-position of pyridine derivatives. Usually the halogen atoms at the 2/6 positions of pyridine *N*-oxides are more reactive relative to those at other positions and thus can be preferentially transformed into other functionalities.[9] The highly reactive halogen atoms at the 2-position of pyridine *N*-oxides can also react with Grignard reagents in two ways based on previous reports: (1) the replacement of chlorine by the R- or Ar-group of Grignard reagents[10] and (2) the exchange reaction between bromine and magnesium.[11] Due to these reactions, direct arylation or alkylation of 2-halopyridine *N*-oxides using Grignard reagents to obtain the corresponding 6-substituted 2-halopyridine *N*-oxides can be remarkably challenging, and to the best of our knowledge, there has been no report on such functionalizations to date.[12] Recently we have discovered a facile condition for the arylation and alkylation of nitropyridine *N*-oxides with Grignard reagents.[3b] We rationalize that the mild procedure with high chemoselectivity may be suitable for the desired functionalization of 2-halopyridine *N*-oxides.

In a preliminary experiment, a complex mixture was obtained when 2-chloro-3-ethoxycarbonyl-pyridine *N*-oxide (**1a**) was treated with PhMgBr or EtMgBr at −50 °C and quenched with water. A similar result was obtained when the reactions were worked up by heating the resulting mixture in DMF or Ac_2O.[3f] The complexity of the products could be due to the instability of the chlorine-containing adduct dihydropyridine *N*-oxides under those workup conditions, and next we attempted to aromatize the dihydropyridine *N*-oxides into the corresponding pyridine *N*-oxides *in situ* using DDQ.[13] As expected, the desired 2-chloro-3-ethoxycarbonyl-6-phenylpyridine *N*-oxide (**3aa**) and 2-chloro-3-ethoxycarbonyl-6-ethylpyridine *N*-oxide (**3ae**) were obtained in 83% and 95%, respectively (Table 1, entries 1 and 5). This finding demonstrated that the pyridine *N*-oxides bearing an electron-withdrawing group were sufficiently reactive for the nucleophilic addition of Grignard reagents,

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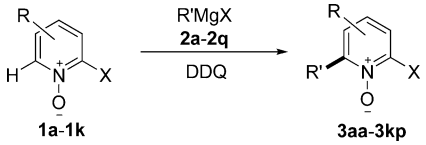
Table 1. Arylation, Alkenylation, and Alkylation of Functionalized 2-Chloro- or Bromopyridine *N*-Oxides with Various Grignard Reagents[a]



entry	1 (X, R)	2 (R′)	product	yield[b] (%)
1	**1a** (Cl, 3-COOMe)	**2a** (Ph)	**3aa**	83
2	**1a**	**2b** (2-MeOC$_6$H$_4$)	**3ab**	91
3	**1a**	**2c** (2-MeOOCC$_6$H$_4$)	**3ac**	87
4	**1a**	**2d** (thiophen-2-yl)	**3ad**	93
5	**1a**	**2e** (Et)	**3ae**	95
6	**1a**	**2f** (*n*-Bu)	**3af**	98
7	**1a**	**2g** (cyclopentyl)	**3ag**	98
8	**1a**	**2h** (vinyl)	**3ah**	76
9	**1a**	**2i** (styryl)	**3ai**	78
10	**1b** (Cl, 4-COOMe)	**2f**	**3bf**	90
11	**1c** (Cl, 5-COOMe)	**2a**	**3ca**	68
12	**1d** (Cl, 3-CN)	**2j** (3-CF$_3$C$_6$H$_4$)	**3dj**	96
13	**1d**	**2g**	**3dg**	88
14	**1e** (Cl, 5-PhCO)	**2k** (4-MeC$_6$H$_4$)	**3ek**	85
15	**1e**	**2l** (*i*-Pr)	**3el**	78
16	**1f** (Cl, 3-CH$_3$CO)	**2c**	**3 fc**	75
17	**1f**	**2m** (prop-1-enyl)	**3fm**	86
18	**1f**	**2n** (cyclohexyl)	**3fn**	90
19	**1g** (Cl, 3-NO$_2$)	**2p** (4-FC$_6$H$_4$)	**3gp**	90
20	**1h** (Br, 3-COOMe)	**2q** (*n*-Pr)	**3hq**	65
21	**1h**	**2m**	**3hm**	70
22	**1i** (Br, 4-COOMe)	**2b**	**3ib**	72
23	**1i**	**2f**	**3if**	78
24	**1i**	**2h**	**3ih**	70
25	**1j** (Br, 5-PhCO)	**2p**	**3jp**	75
26	**1j**	**2q**	**3jq**	75
27	**1k** (Br, 4-NO$_2$-5-Br)	**2d**	**3kd**	80
28	**1k**	**2p**	**3kp**	82

[a]2-Halopyridine *N*-oxide was treated with Grignard reagent (1.2 equiv) in THF at −50 °C. After the addition reaction was completed (1−3 h), DDQ (1.2 equiv) was added. The mixture was allowed to warm to room temperature and stirred for additional 4−6 h. [b]Yield of isolated product.

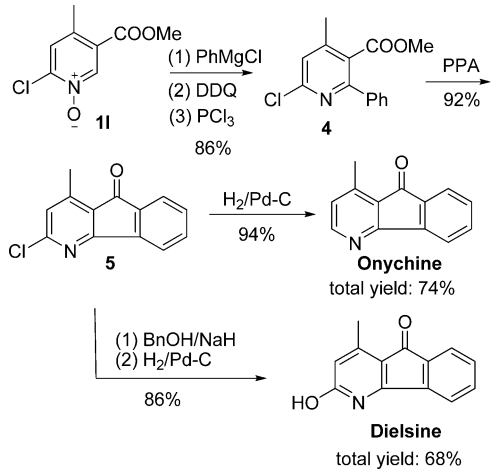
and it is critical to choose appropriate workup conditions for the conversion of the adduct dihydropyridine *N*-oxides into more stable pyridine *N*-oxides.

The above reaction represents a very simple yet highly efficient protocol for arylation and alkylation of 2-halopyridine *N*-oxides. It was thus further explored with the results summarized in Table 1. For the functionalized 2-chloropyridine *N*-oxides (**1a**−**1g**), arylation, alkenylation, and alkylation with Grignard reagents went smoothly (Table 1, entries 1−19), and neither the deprotonation at the 6-position[14] nor the displacement of Cl with R′ group[10] was observed. Notably the functionalized 2-bromopyridine *N*-oxides (**1h**−**1k**) could be readily arylated, alkenylated, and alkylated as well (Table 1, entries 20−28).

Interestingly, heteroaryl or functionalized aryl magnesium reagents could also be used for the corresponding arylation, leading to the expected products in 75−93% yields (Table 1, entries 3, 4, 12, 16, and 27). Overall the reactions also showed a remarkable tolerance toward different functional groups such as ester (**1a**−**1c**, **1h**, **1i**), cyano (**1d**), or nitro group (**1g** and **1k**). Besides, the highly functionalized oxide, 2,5-dibromo-4-nitropyridine *N*-oxide (**1k**), could also be arylated with Grignard reagents (Table 1, entries 27 and 28). Even more interesting is the fact that the arylation, alkenylation, and alkylation with Grignard reagents proceeded smoothly in the presence of a ketone group such as CH$_3$CO and PhCO (Table 1, entries 14−18, 25, and 26). The selective addition of Grignard reagents to C2 or C6 of pyridine *N*-oxides in the presence of a ketone group has been observed for the first time, and this should help to further understand and better utilize the high reactivity of pyridine *N*-oxides toward the nucleophilic addition of Grignard reagents.

Compared with many transition-metal-catalyzed C−H activation reactions, the procedure described herein had the advantage that an efficient arylation, alkenylation, or alkylation of pyridine *N*-oxides could be achieved in the presence of activated C−Cl or C−Br bonds. Hence it can provide a solution to the problem of C2/C6 regioselective functionalization of pyridine derivatives by using Cl or Br as a blocking group that could then be removed or transformed into other desired groups. To further probe its synthetic potentials, total syntheses of two natural products (onychine[15] and dielsine[16]) and PARP-1 inhibitor GPI 16539[17] using this method as the key step are outlined in Schemes 1 and 2. In Scheme 1, methyl

Scheme 1. Total Syntheses of Onychine and Dielsine



2-chloro-4-methyl-5-nicotinate *N*-oxide (**1l**) was phenylated and deoxygenated in one pot to give methyl 2-chloro-4-methyl-6-phenyl-5-nicotinate (**4**) in 86% yield. Compound **4** was annulated with PPA to afford the key precursor (**5**) to onychine and dielsine. The chlorine atom of **5**, which was originally fixed as a blocking group,[18] was later removed or translated into hydroxyl group to furnish onychine and dielsine in a total yield of 74% or 68%, respectively.

The reported total synthesis of PARP-1 inhibitor GPI 16539 started with a nonregioselective Suzuki coupling of 2,6-dichloro-3-nitropyridine with 2-diisopropylcarbamoylphenylboronic acid leading to the mixture of the desired 2-arylated intermediate in 42% and the other isomer in 38%, and the target molecule was obtained in only 14% overall yield.[17b,19] By using our protocol (Scheme 2) a facile arylation of readily available 2-chloro-5-nitropyridine *N*-oxide (**1m**) with 2-methoxycarbonylphenylmagnesium chloride[20] afforded the

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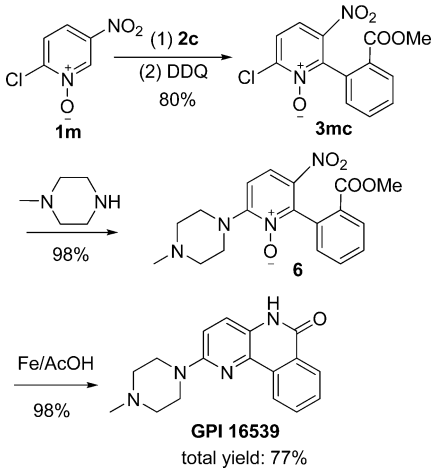
Scheme 2. Total Synthesis of PARP-1 Inhibitor GPI 16539



desired arylated product (**3mc**) in 80% yield. Displacement of the chlorine atom of the intermediate **3mc** with *N*-methylpiperazine gave the key precursor **6**, which was subjected to reduction with iron powder yielding GPI 16539. This total synthesis involved only three steps, and the overall yield was 77%. Here the reagents used in our syntheses are readily available, and corresponding procedures were very straightforward. Once again this total synthesis has demonstrated that the problem of C2/C6 regioslective functionalization of pyridine derivatives could be circumvented by using Cl or Br as a blocking group, which could be readily transformed into other substituents.

In summary, we have developed a one-pot arylation, alkenylation, and alkylation of 2-chloro or bromopyridine *N*-oxides with various Grignard reagents. Since highly reactive halogen atoms can seldom be tolerated in many known transition-metal-catalyzed couplings and direct C−H functionalization, the procedure described herein can be viewed as a highly selective C−H functionalization of pyridine *N*-oxides in the presence of reactive Cl or Br atoms. In addition, these halogen atoms were used as an easily transformable blocking group and thus provide a general and practicable approach to circumvent the problem of C2/C6 regioslective functionalization of pyridine derivatives. Given the simplicity, efficiency, and tolerance toward functional groups such as ester, cyano, nitro, and ketone groups, this protocol can find wide applications in building various pyridine compounds including pyridine-based natural products and bioactive complex molecules.

EXPERIMENTAL SECTION

General Procedure for Arylation, Alkenylation, and Alkylation of Functionalized 2-Halopyridine *N*-Oxides with Grignard Reagents. A dry argon-flushed 250-mL flask, equipped with a magnetic stirrer and a septum, was charged with 2-halopyridine *N*-oxide[21] (3.2 mmol). Dry THF (80 mL) was added, the resulting solution was cooled to −50 °C, and RMgX (3.8 mmol, titrated before use[22]) was then added slowly using a syringe during 1 h. The mixture was stirred at that temperature for 1−1.5 h until the 2-halopyridine *N*-oxide was consumed (checked by TLC). DDQ (860 mg, 3.8 mmol) was added. The mixture was then allowed to come to room temperature and stirred for 4 h. The reaction was quenched with a 20% solution of Na_2CO_3 (20 mL), and THF was removed by distillation in vacuo. The aqueous phase was extracted with CH_2Cl_2 (5 × 40 mL), and the organic fractions were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography to yield the desired oxide.

3aa. Yield 437 mg, 83%; mp = 148−149 °C; IR (cm^{-1}, KBr) 1729; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.82 (m, 2H), 7.70 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 3.2 Hz, 3H), 7.42 (d, J = 8.3 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8, 131.9, 130.5, 129.4, 129.1, 129.0, 128.7, 128.4, 126.6, 125.9, 123.9, 120.3, 51.6; MS (ESI) $[M + H]^+$ (m/z, 264). Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 58.97; H, 3.65; N, 5.17.

3ab. Yield 534 mg, 91%; mp = 125−128 °C; IR (cm^{-1}, KBr) 1736; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 1H), 7.49−7.45 (m, 1H), 7.40−7.36 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 4.00 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 157.3, 151.7, 143.1, 131.7, 130.5, 128.8, 125.3, 125.1, 121.5, 120.6, 111.4, 55.9, 53.3; MS (ESI) $[M + H]^+$ (m/z, 294). Anal. Calcd for $C_{14}H_{12}ClNO_4$: C, 57.25; H, 4.12; N, 4.77. Found: C, 56.98 H, 3.91; N, 4.56.

3ac. Yield 559 mg, 87%; mp = 138−140 °C; IR (cm^{-1}, KBr) 1732; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.7 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.67−7.63 (m, 1H), 7.59−7.55 (m, 1H), 7.35−7.32 (m, 2H), 4.00 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 163.5, 153.9, 142.6, 132.9, 132.4, 131.1, 130.2, 130.0, 129.9, 128.7, 126.0, 125.9, 122.9, 53.2, 52.4; MS (ESI) $[M + H]^+$ (m/z, 322). Anal. Calcd for $C_{15}H_{12}ClNO_5$: C, 55.99; H, 3.73; N, 4.35. Found: C, 55.81; H, 3.86; N, 4.28;

3ad. Yield 501 mg, 93%; mp = 123−125 °C; IR (cm^{-1}, KBr) 1736; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.94 (m, 2H), 7.81 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 5.0 Hz, 1H), 7.29−7.26 (m, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 146.3, 143.3, 133.1, 131.2, 129.4, 126.8, 126.6, 125.2, 118.6, 53.2; MS (ESI) $[M + H]^+$ (m/z, 270). Anal. Calcd for $C_{11}H_8ClNO_3S$: C, 48.99; H, 2.99; N, 5.19. Found: C, 48.70; H, 2.79; N, 4.94.

3ae. Yield 409 mg, 95%; mp = 115−116 °C; IR (cm^{-1}, KBr) 1735; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 3.98 (s, 3H), 3.03 (q, J = 7.4 Hz, 2H), 1.35 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 155.7, 142.5, 125.3, 124.4, 122.0, 53.0, 24.6, 10.4; MS (ESI) $[M + H]^+$ (m/z, 216). Anal. Calcd for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 49.89; H, 4.49; N, 6.34.

3af. Yield 477 mg, 98%; mp = 66−67 °C; IR (cm^{-1}, KBr) 1739; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 3.97 (s, 3H), 2.99 (t, J = 7.7 Hz, 2H), 1.73 (m, J = 7.6 Hz, 2H), 1.45 (m, J = 7.4 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 157.0, 142.8, 127.5, 125.8, 121.8, 53.2, 31.5, 27.8, 22.5, 13.8; MS (ESI) $[M + H]^+$ (m/z, 244). Anal. Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; N, 5.75. Found: C, 53.98; H, 5.61; N, 5.60.

3ag. Yield 501 mg, 98%; mp = 92−93 °C; IR (cm^{-1}, KBr) 1728; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 1.0 Hz, 1H), 3.97 (s, 3H), 3.78 (m, 1H), 2.29−2.22 (m, 2H), 1.81−1.75 (m, 4H), 1.62−1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 160.6, 142.8, 127.1, 125.7, 119.7, 53.2, 53.1, 40.8, 30.7, 25.3; MS (ESI) $[M + H]^+$ (m/z, 256). Anal. Calcd for $C_{12}H_{14}ClNO_3$: C, 56.37; H, 5.52; N, 5.48. Found: C, 56.11; H, 5.39; N, 5.31.

3ah. Yield 325 mg, 76%; mp = 75−76 °C; IR (cm^{-1}, KBr) 1732, ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.39 (dd, J_1 = 11.3 Hz, J_2 = 18.2 Hz, 1H), 6.20 (d, J = 17.8 Hz, 1H), 5.80 (d, J = 11.3 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 151.2, 143.1, 127.9, 125.6, 123.7, 119.6, 53.2; MS (ESI) $[M + H]^+$ (m/z, 214). Anal. Calcd for $C_9H_8ClNO_3$: C, 50.47, H, 3.74; N, 6.54. Found: 50.37; H, 3.72, N, 6.47.

3ai. Yield 452 mg, 78%; mp = 110−122 °C; IR (cm^{-1}, KBr) 1739; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 16.6 Hz, 1H), 7.68−7.58 (m, 5H), 7.41−7.37 (m, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 151.3, 138.4, 135.7, 129.9, 129.0, 127.8, 125.7, 119.4, 118.6, 53.2; MS (ESI) $[M + H]^+$ (m/z, 290). Anal. Calcd for $C_{15}H_{12}ClNO_3$: C, 62.19; H, 4.17; N, 4.83. Found: C, 61.89; H, 4.10; N, 4.73.

3bf. Yield 438 mg, 90%; mp = 55−56 °C; IR (cm^{-1}, KBr) 1723; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 3.96 (s, 3H), 2.96 (t, J = 7.7 Hz, 2H), 1.74−1.69 (m, 2H),

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1.49−1.42 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 154.7, 142.6, 125.2, 124.4, 122.9, 53.0, 31.1, 27.9, 22.5, 13.8; MS (ESI) $[M + H]^+$ (m/z, 244). Anal. Calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; N, 5.75. Found: C, 53.96; H, 5.60; N, 5.89.

3ca. Yield 358 mg, 68%; mp = 79−81 °C; IR (cm^{-1}, KBr) 1738; ^{1}H NMR (400 MHz, $CDCl_3$): 7.63−7.58 (m, 2H), 7.49−7.47 (m, 3H), 7.42−7.39 (m, 2H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 151.6, 145.4, 131.4, 129.7, 129.5, 129.1, 128.3, 125.4, 125.0, 52.8; MS (ESI) $[M + H]^+$ (m/z, 264). Anal. Calcd for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 58.96; H, 3.67; N, 5.13.

3dj. Yield 573 mg, 96%; mp = 123−126 °C; IR (cm^{-1}, KBr) 2246; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 146.2, 132.6, 131.7, 131.4, 131.1, 129.2, 127.8, 127.7, 127.4, 126.4, 126.3, 126.3, 126.2, 125.0, 124.8, 122.3, 113.0; MS (ESI) $[M + H]^+$ (m/z, 299). Anal. Calcd for $C_{13}H_6ClF_3N_2O$: C, 52.28; H, 2.03; N, 9.38. Found: C, 51.98; H, 1.87; N, 9.12.

3dg. Yield 392 mg, 88%; mp = 151−153 °C; IR (cm^{-1}, KBr) 2236; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 3.76 (m, J = 8.3 Hz, 1H), 2.29−2.22 (m, 2H), 1.84−1.74 (m, 4H), 1.63−1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 144.9, 127.3, 120.8, 113.4, 110.8, 40.7, 30.7, 25.3; MS (ESI) $[M + H]^+$ (m/z, 223). Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.04; H, 4.72; N, 12.29.

3ek. Yield 550 mg, 85%; mp = 211−212 °C; IR (cm^{-1}, KBr) 1682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.59 (m, 3H), 7.48 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.8 Hz, 2H), 7.27−7.23 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 149.8, 144.1, 140.1, 136.9, 135.8, 133.8, 130.1, 129.7, 128.9, 128.5, 127.2, 125.3, 123.7, 21.4; MS (ESI) $[M + H]^+$ (m/z, 324). Anal. Calcd for $C_{19}H_{14}ClNO_2$: C, 70.48; H, 4.36; N, 4.33. Found: C, 70.19; H, 4.02; N, 4.07.

3el. Yield 430 mg, 78%; mp = 116−117 °C; IR (cm^{-1}, KBr) 1668; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.69−7.65 (m, 1H), 7.54−7.47 (m, 3H), 6.99 (d, J = 8.3 Hz, 1H), 3.38−3.31 (m, 1H), 1.37 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 155.9, 144.0, 136.0, 135.9, 134.6, 130.2, 129.0, 123.9, 122.8, 31.7, 17.7; MS (ESI) $[M + H]^+$ (m/z, 276). Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34, H, 5.12, N, 5.08. Found: C, 65.53; H, 5.19, N, 4.86.

3 fc. Yield 458 mg, 75%; mp = 143−144 °C; IR (cm^{-1}, KBr) 1726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.7 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 3.79 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 166.5, 153.3, 140.1, 136.9, 132.4, 131.0, 131.3, 130.1, 129.9, 124.1, 123.5, 52.5, 30.3; MS (ESI) $[M + H]^+$ (m/z, 306). Anal. Calcd for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; N, 4.58. Found: C, 58.71; H, 4.02; N, 4.38;

3fm. Yield 364 mg, 86%; mp = 102−103 °C; IR (cm^{-1}, KBr) 1700; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 18.0 Hz, 1H), 6.82−6.73 (m, 1H), 2.68 (s, 3H), 2.04 (d, J = 5.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 150.9, 140.8, 137.6, 135.1, 124.1, 122.4, 120.0, 30.4, 18.4; MS (ESI) $[M + H]^+$ (m/z, 212). Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 57.01; H, 4.82, N, 6.47.

3fn. Yield 456 mg, 90%; mp = 75−76 °C; IR (cm^{-1}, KBr) 1712; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 3.53 (dd, J = 2.8 Hz, J = 13.6 Hz, 1H), 2.67 (s, 3H), 2.08 (d, J = 13.6 Hz, 2H), 1.88 (d, J = 13.2 Hz, 2H), 1.80−1.46 (m, 2H), 1.33−1.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 160.0, 140.0, 135.4, 123.8, 120.4, 38.5, 30.4, 30.2, 26.1, 26.0; MS (ESI) $[M + H]^+$ (m/z, 254). Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.68; H, 6.33; N, 5.49.

3gp. Yield 483 mg, 90%; mp = 149−151 °C; IR (cm^{-1}, KBr) 1531, 1346; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.84 (m, 2H), 7.78 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.22 (t, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 162.9, 152.6, 146.1, 139.3, 131.7, 127.0, 123.3, 119.8, 116.0, 115.8; MS (ESI) $[M + H]^+$ (m/z, 269). Anal. Calcd for $C_{11}H_6ClFN_2O_3$: C, 49.18; H, 2.25; N, 10.43. Found: C, 48.94; H, 1.99; N, 10.26.

3hq. Yield 356 mg, 65%; mp = 79−80 °C; IR (cm^{-1}, KBr) 1735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 6.8 Hz, 1H), 3.97 (s, 3H), 2.98 (t, J = 7.5 Hz, 2H), 1.83−1.74 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 156.4, 134.4, 130.9, 125.3, 122.7, 53.2, 19.1, 13.8; MS (ESI) $[M + H]^+$ (m/z, 275). Anal. Calcd for $C_{10}H_{12}BrNO_3$: C, 43.82; H, 4.41; N, 5.11. Found: C, 43.81; H, 4.44; N, 5.01.

3hm. Yield 381 mg, 70%; mp = 102−103 °C; IR (cm^{-1}, KBr) 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H),7.13 (d, J = 16.2 Hz, 1H), 6.81−6.72 (m, 1H), 3.97 (s, 3H), 2.44 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 151.1, 137.5, 134.8, 130.2, 125.3, 122.8, 120.2, 53.1, 18.4; MS (ESI) $[M + H]^+$ (m/z, 273). Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14, H, 3.70, N, 5.15. Found: C, 43.85; H, 3.58; N, 5.01.

3ib. Yield 487 mg, 72%; mp = 125−127 °C; IR (cm^{-1}, KBr) 1731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.10 (m, 1H), 7.93−7.90 (m, 1H), 7.48−7.44 (m, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 157.3, 149.6, 131.6, 130.5, 129.5, 126.9, 126.2, 125.7, 124.8, 120.6, 111.2, 55.8, 52.9; MS (ESI) $[M+Na]^+$ (m/z, 361). Anal. Calcd for $C_{14}H_{12}BrNO_4$: C, 49.73; H, 3.58; N, 4.14. Found: C, 49.48; H, 3.41; N, 3.98.

3if. Yield 449 mg, 78%; mp = 55−56 °C; IR (cm^{-1}, KBr) 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 1.8 Hz, 1H), 7.80 (s, 1H), 3.95 (s, 3H), 2.96 (t, J = 7.7 Hz, 2H), 1.76−1.68 (m, 2H), 1.50−1.41 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 154.5, 133.5, 128.2, 125.3, 124.4, 122.9, 52.9, 31.5, 28.0, 22.5, 13.8; MS (ESI) M^+ (m/z, 288). Anal. Calcd for $C_{11}H_{14}BrNO_3$: C, 45.85, H, 4.90; N, 4.86. Found: C, 45.65; H, 4.75; N, 4.77.

3ih. Yield 361 mg, 70%; mp = 79−80 °C; IR (cm^{-1}, KBr) 1728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.33 (dd, J_1 = 17.8 Hz, J_2 = 11.4 Hz, 1H), 6.19 (dd, J_1 = 17.8 Hz, J_2 = 6.3 Hz, 1H), 5.75 (dd, J_1 = 11.3 Hz, J_2 = 8.8 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 149.5, 133.7, 128.6, 127.8, 125.4, 122.6, 121.9, 52.9; MS (ESI) $[M + H]^+$ (m/z, 259). Anal. Calcd for $C_9H_8BrNO_3$: C, 41.89; H, 3.12; N, 5.43. Found: C, 41.66; N, 3.07; N, 5.38.

3jp. Yield 558 mg, 75%; mp = 134−137 °C; IR (cm^{-1}, KBr) 1672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.40−7.32 (m, 4H), 7.22 (d, J = 8.3 Hz, 1H), 6.93 (t, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 164.6, 162.1, 148.5, 137.8, 135.6, 134.1, 132.5, 132.4, 129.6, 129.5, 128.7, 126.3, 124.5, 115.5, 115.3; MS (ESI) M^+ (m/z, 372). Anal. Calcd for $C_{18}H_{11}BrFNO_2$: C, 58.09; H, 2.98; N, 3.76. Found: C, 57.83; H, 2.79; N, 3.58.

3jq. Yield 480 mg, 75%; IR (cm^{-1}, KBr) 1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.4 Hz, 2H), 7.67 (t, J = 7.2 Hz, 2H), 7.52 (t, J = 7.6 Hz, 2H), 7.00 (t, J = 8.8 Hz, 1H), 2.90 (t, J = 7.7 Hz, 2H), 1.78−1.66 (m, 2H), 0.96−0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 153.3, 136.3, 135.9, 134.5, 130.2, 129.1, 129.0, 127.5, 123.4, 58.5, 31.7, 19.7, 14.2; MS (ESI) $[M + H]^+$ (m/z, 321). Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27; H, 4.41; N, 4.37; Found: C, 56.49; H, 4.42; N, 4.29.

3kd. Yield 608 mg, 80%; mp = 140−141 °C; IR (cm^{-1}, KBr) 1547, 1357; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.70 (dd, J = 5.0 Hz, J = 0.8 Hz, 1H), 7.56 (dd, J_1 = 1.6 Hz, J_2 = 0.8 Hz, 1H), 7.21 (dd, J_1 = 5.0 Hz, J_2 = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.5, 132.8, 132.7, 130.7, 130.5, 126.5, 123.5, 113.9; MS (ESI) $[M + H]^+$ (m/z, 381). Anal. Calcd for $C_9H_4Br_2N_2O_3S$: C, 28.45, H, 1.06; N, 7.37. Found: C, 28.18; H, 1.09; N, 7.30.

3kp. Yield 621 mg, 82%; mp = 197−198 °C; IR (cm^{-1}, KBr) 1547, 1347; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.37−7.34 (m, 2H), 7.27−7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 162.5, 152.7, 143.8, 132.9, 131.6, 131.5, 127.9, 124.5, 116.5, 114.1; MS (ESI) $[M + H]^+$ (m/z, 392). Anal. Calcd for $C_{11}H_5Br_2FN_2O_3$: C, 33.71; H, 1.29; N, 7.15. Found: C, 33.49; H, 1.03; N, 6.98.

3mc. Yield 984 mg, 80% mp = 133−134 °C; IR (cm^{-1}, KBr) 1722, 1536, 1349; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (dd, J = 0.8

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Hz, 7.68 Hz, 1H), 7.87 (d, J = 9.1 Hz, 1H), 7.71−7.61 (m, 3H), 7.24 (d, J = 0.8 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 148.9, 146.7, 145.2, 133.4, 131.0, 130.6, 130.4, 129.5, 128.8, 124.7, 119.7, 52.5; MS (ESI) $[M + H]^+$ (m/z, 309). Anal. Calcd for $C_{13}H_9ClN_2O_5$: C, 50.58; H, 2.94; N, 9.08. Found: C, 50.73; H, 3.09; N, 9.02.

4. A solution of **1l** (10 mmol) in THF (250 mL) was treated with phenyl magnesium chloride (**2a**, 12 mmol) and then DDQ (15 mmol) as described in the general procedure. Upon completion of the reaction (monitored by TLC), the mixture was warmed to 0 °C, and PCl_3 (15 mmol) was added dropwise. The mixture was allowed to come to room temperature and stirred for 2 h. The mixture was treated with saturated aqueous Na_2CO_3 solution (80 mL), and THF was removed by distillation in vacuo. The aqueous phase was extracted with CH_2Cl_2 (5 × 80 mL), and the organic fractions were dried (Na_2CO_3) and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give **4** in 86% yield (2.30g): white solid, mp = 94−95 °C; IR (cm^{-1}, KBr) 1730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.35−7.33 (m, 3H), 7.12 (s, 1H), 3.58 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 156.2, 150.4, 147.9, 137.5, 128.2, 127.4, 127.2, 126.7, 122.6, 51.4, 18.4; MS (ESI) $[M + H]^+$ (m/z, 262). Anal. Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62, N, 5.35. Found: C, 64.43; H, 4.46; N, 5.54.

5.[16b] Compound **4** (300 mg, 1.2 mmol) was dissolved in 12 mL of PPA and heated at 210 °C until the reaction was completed (checked by TLC). The mixture was poured onto ice and neutralized with saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL), and the organic fractions were dried (Na_2CO_3) and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 10:2) to give **5** in 92% yield (242 mg): white solid, mp = 190−191 °C; IR (cm^{-1}, KBr) 1714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.04 (s, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 166.4, 155.8, 149.9, 141.9, 135.1, 135.0, 131.4, 125.4, 124.6, 123.9, 131.3, 17.3; MS (ESI) $[M + H]^+$ (m/z, 230). IR, NMR, and MS data was consistent with that reported in the literature.[16b]

Onychine.[15b] Compound **5** (103 mg, 0.45 mmol) was dissolved in CH_3OH (15 mL). Anhydrous sodium acetate (410 mg, 0.5 mmol) and palladium on carbon (10%, 100 mg) were added, and the mixture was stirred under 1 atm of H_2 at ambient temperature. After compound **5** was consumed (monitored by TLC), the reaction mixture was filtered and evaporated to dryness. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to give the title product in 94% yield (82 mg): white solid, mp = 100−102 °C; IR (cm^{-1}, KBr) 1668; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 5.3 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 5.3 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.2, 165.6, 152.8, 147.7, 143.1, 135.1, 135.0, 130.9, 126.0, 125.9, 123.7, 120.8, 17.3; MS (ESI) $[M + H]^+$ (m/z, 196). Data was consistent with that reported in the literature.[15b]

Dielsine.[16b] NaH (22 mg, 0.9 mmol) was dissolved in a solution of phenylmethanol (146 mg, 1.35 mmol) in DMF (15 mL), and compound **5** (103 mg, 0.45 mmol) was added. The mixture was heated at 70——90 °C until compound **5** was consumed (monitored by TLC). To the resulting mixture were added acetic acid (60 mg, 1.0 mmol) and palladium on carbon (10%, 100 mg), and the mixture was stirred under 1 atm of H_2 at ambient temperature. Upon completion of the debenzylation (monitored by TLC), the mixture was filtered and evaporated to dryness. The residue was purified by column chromatography (ethyl acetate) to give the title product in 86% yield (82 mg): white solid, mp > 300 °C; IR (cm^{-1}, KBr) 1701, 1638; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−7.85 (m, 1H); 7.59−7.02 (m, 4H); 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 165.4, 154.4, 150.2, 141.0, 135.5, 134.5, 131.8, 125.5, 124.2, 123.7, 120.9, 16.6; MS (ESI) M^+ (m/z, 211). Data was consistent with that reported in the literature.[16b]

6. To a solution of **3mc** (500 mg, 1.6 mmol) in THF (20 mL) were added triethylamine (0.3 mL, 2.1 mmol) and *N*-methyl-piperazine (0.4 mL, 3.6 mmol). The mixture was stirred and heated at reflux until the compound **3mc** was consumed (monitored by TLC). After evaporation to dryness in vacuo, the residue was taken up with CH_2Cl_2 (300 mL) and washed with saturated aqueous Na_2CO_3 solution (25 mL). The organic fractions were dried (Na_2CO_3) and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 1:2) to give **6** in 98% yield (591 mg): yellow solid, mp > 220 °C (dec); IR (cm^{-1}, KBr) 1720, 1565, 1334; ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.08 (t, J = 9.8 Hz, 2H), 7.70 (d, J = 6.1 Hz, 1H), 7.62 (d, J = 6.4 Hz, 1H), 7.33(d, J = 6.6 Hz, 1H), 7.26 (d, J = 8.7 Hz, 1H), 3.66 (s, 3H), 3.37 (br s, 4H), 2.51 (br s, 4H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 165.4, 156.9, 147.2, 138.8, 133.1, 132.6, 129.8, 129.2, 121.9, 112.2, 55.9, 53.9, 52.1, 46.7, 45.5, 18.5; MS (ESI) $[M + H]^+$ (m/z, 373). Anal. Calcd for $C_{18}H_{20}N_4O_5$: C, 58.06; H, 5.41; N, 15.05. Found: C, 58.21; H, 5.62; N, 15.32.

GPI 16539.[17b] Compound **6** (150 mg, 0.4 mmol) was dissolved in acetic acid (20 mL), and iron powder (200 mg, 3.6 mmol) was added. The mixture was stirred and heated at 100 °C until the reaction was completed (monitored by TLC). The resulting mixture was neutralized with saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (5 × 80 mL), and the organic fractions were dried (Na_2CO_3) and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate) to give the title compound in 98% yield (110 mg): yellow solid, mp = 280−283 °C; IR (cm^{-1}, KBr) 1656; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H); 8.71 (d, J = 8.0 Hz, 1H); 8.43 (d, J = 7.9 Hz, 1H); 7.77 (t, J = 8.0 Hz, 1H); 7.60 (t, J = 8.0 Hz, 1H); 7.42 (d, J = 9.0 Hz, 1H); 6.85 (d, J = 9.0 Hz, 1H); 3.65 (s, 4H); 2.56 (s, 4H); 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 155.4, 135.9, 134.0, 132.5, 128.7, 127.5, 127.0, 126.5, 124.7, 123.8, 109.7, 54.9, 46.3, 45.7; MS (ESI) $[M + H]^+$ (m/z, 295). Data was consistent with that reported in the literature.[17b]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General information and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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