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Pd/Cu-Catalyzed Direct Alkenylation of Azole Heterocycles with Alkenyl Halides

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Dedicated to the memory of Dr. Keith Fagnou

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Direct alkenylation of azole heterocycles through Pd–Cu-catalyzed C–H bond activation has been reported using alkenyl bromides as the coupling partners. The reaction enables the introduction of various mono-, di-, or trisubstituted alkenyl bromides as well as a benzyl chloride to the caffeine core.

Introduction

Direct transition-metal-catalyzed functionalization of C–H bonds in heterocycles has received significant attention in modern organic chemistry due to its atom economy, high functional group tolerance, and the possibilities for transformation of the unreactive C–H bonds into diverse functions in one operation. In particular, direct arylation of heterocycles has already gained widespread acceptance within the synthetic community, because of its capacity to utilize simpler and cheaper precursors for the construction of complex frameworks.[1] In contrast to the much more developed palladium-catalyzed C–H arylation reaction of various heterocycles, direct alkenylations of heteroaromatics with vinyl halides have received much less attention. In these instances, a very few number of heterocycles were studied. Grierson et al.[2] reported direct alkenylation of 5-phenyloxazoles with (*E*)-β-bromostyrenes under copper catalysis. Other groups have extended this methodology to the palladium-catalyzed alkenylation of other oxazoles, including 5-aryloxazoles[3] and ethyl oxazole-4-carboxylate.[4] In 2008, Doucet et al.[5] successfully accomplished the palladium-catalyzed direct C–H bond activation of benzoxazole and benzothiazole[2] with alkenyl bromides. More recently, other groups demonstrated that the palladium-catalyzed direct C–H alkenylation of imidazopyridines,[6] sydnones,[7] and *N*-iminopyridinium ylides[8] can be successfully achieved. Although these processes can compensate for the conventional coupling processes, they still suffer from some deficiencies. First, most methods allow the alkenylation of only a few types of heterocycles, thus limiting the scope and generality of the methodologies. Second, in most cases studied, specific conditions are often required for every heterocycle to be successfully alkenylated. Thus, the development of new and general catalyst systems for this type of transformation is strongly desired.

During our recent studies on the metal-catalyzed direct arylation reaction of free-(NH_2) adenines,[9] we reported a preliminary result where the newly developed catalytic system also enabled, for the first time, efficient Pd–Cu-catalyzed direct vinylation of free-(NH_2) adenine with β-(*E*)-bromostyrene in a satisfactory 55% yield under ligandless conditions. It should be noted that both palladium and copper catalysts are necessary to achieve this transformation. In pursuit of our efforts to further extend the scope of the functionalization of heteroaromatics via C–H bond activation, combined with our interest to discover news hsp90[10] inhibitors,[11] we herein report a novel method for the direct Pd–Cu-catalyzed alkenylation of various heterocycles, including xanthines, free-(NH_2) adenines, benzimidazoles, benzoxazoles, benzothiazoles, and thiazoles with various alkenyl bromides. This new approach provides straightforward and general access to a wide variety of alkenyl heterocycles, which would be useful due to their significant biological importance.[12]

Results and Discussion

Initial investigations were performed by coupling caffeine (**1a**) with 1-bromo-2-methylpropene (**2a**) as model substrates by using $Pd(OAc)_2$ (10 mol-%) and P(*o*-tolyl)$_3$ (20 mol-%); *t*BuOLi (2 equiv.) was added as a base in dioxane, and the mixture was heated in a sealed tube at 110 °C for 16 h. Satisfyingly, these preliminary conditions appeared

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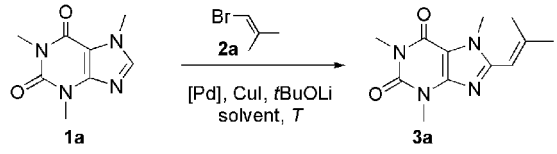
to be efficient for the direct alkenylation of **1a**; however, only moderate conversion was observed (68%; Table 1, Entry 1). By adding a catalytic amount of CuI (20 mol-%), the conversion of **1a** dramatically increased, and **3a** was obtained in a good 67% yield (Table 1, Entry 2). It should be noted that both palladium and copper catalysts are necessary to achieve this transformation, as no reaction occurred when carrying out the C–H alkenylation in the presence of CuI but without a palladium catalyst. The catalytic activity of $Pd(acac)_2$ proved to be similar to that of $Pd(OAc)_2$, leading to **3a** in a slightly better yield (72%; Table 1, Entry 3). The use of other palladium sources, however, did not promote the C–H alkenylation reaction or induced a lowering of the conversion rate (Table 1, Entries 4–7). As summarized in Table 1, evaluation of ligand sources revealed that P(*o*-tolyl)$_3$ was superior to all other choices (Table 1, Entry 3 vs. Entries 8–13).

Table 1. Optimization of C-alkenylation of 1a with 1-bromo-2-methylpropene.[a]



Entry	[Pd]	Ligand	Solvent	*T* [°C]/ Time [h]	Conv.[b] [%]	Yield[c] [%]
1	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	dioxane	110/16	68[d]	–
2	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	dioxane	110/16	100	67
3	$Pd(acac)_2$	P(*o*-tolyl)$_3$	dioxane	110/16	100	72
4	$Pd(OH)_2/C$	P(*o*-tolyl)$_3$	dioxane	110/16	0	–
5	$PdCl_2$	P(*o*-tolyl)$_3$	dioxane	110/16	59	–
6	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	dioxane	110/16	35	–
7	Pd/C	P(*o*-tolyl)$_3$	dioxane	110/16	<5	–
8	$Pd(acac)_2$	P(2-furyl)$_3$	dioxane	110/16	69	–
9	$Pd(acac)_2$	P(mesityl)$_3$	dioxane	110/16	16	–
10	$Pd(acac)_2$	binap	dioxane	110/16	62	–
11	$Pd(acac)_2$	DPEphos	dioxane	110/16	49	–
12	$Pd(acac)_2$	X-phos	dioxane	110/16	36	–
13	$Pd(acac)_2$	xantphos	dioxane	110/16	65	–
14	$Pd(acac)_2$	P(*o*-tolyl)$_3$	toluene	110/16	100	64
15	$Pd(acac)_2$	P(*o*-tolyl)$_3$	CH_3CN	110/16	42	–
16	$Pd(acac)_2$	P(*o*-tolyl)$_3$	THF	110/16	88	69
17	$Pd(acac)_2$	P(*o*-tolyl)$_3$	THF	130/16	100	86
18	$Pd(acac)_2$	P(*o*-tolyl)$_3$	THF[e]	130/2	100[f]	87[g,h]

[a] Substrate **1a** (1 equiv.), **2a** (1.2 equiv.), and *t*BuOLi (2 equiv.) were heated in a sealed Schlenk tube in the presence of [Pd] (10 mol-%), CuI (20 mol-%), ligand (20 mol-%). [b] The conversion was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and was based on remaining **1a**. [c] Isolated yield. [d] Conversion when the reaction was performed without CuI as co-catalyst. [e] The use of dioxane instead of THF resulted in 83% conversion. [f] A conversion of 47% was obtained when the reaction was performed without CuI as co-catalyst. [g] Yield of **3a** when carrying out the reaction in the presence of $Pd(acac)_2$ (2.5 mol-%), CuI (5 mol-%), and P(*o*-tolyl)$_3$ (5 mol-%). [h] No reaction occurred without palladium catalyst and/or without P(*o*-tolyl)$_3$ ligand.

The screening reaction was continued with respect to the base. The use of *t*BuOLi was found to be optimal, as reactions with Cs_2CO_3, *t*BuOK, K_3PO_4, and Na_2CO_3 were much slower or did not proceed (not shown in Table 1). A brief survey of solvents was therefore undertaken in which ethereal solvents (1,4-dioxane and THF) were found to be the most effective (Table 1, Entries 3 and 16). THF was chosen to evaluate the effect of other parameters on the reaction, including the amount of catalysts, temperature, and reaction time. After a series of assays (not shown in Table 1), the best result was obtained at 130 °C for 2 h by using $Pd(acac)_2$ (2.5 mol-%) and CuI (5 mol-%) as catalysts, P(*o*-tolyl)$_3$ (5 mol-%) as the ligand, and *t*BuOLi (2 equiv.) as the base in THF. Under these conditions, **3a** was formed in 87% yield (Table 1, Entry 18). It should be noted that both palladium and copper catalysts are necessary to achieve successfully this transformation.

With a viable coupling procedure in hand, attention was turned to the generality of the process, and the coupling of alkenyl halides with structurally diverse heterocycles **1a**–**h** was studied (Figure 1). Remarkably, this direct alkenylation reaction appeared to be quite general with respect to different heterocyclic cores (Tables 2 and 3). First, we investigated the scope of the alkenylation reaction of **1a**,**b** with various vinyl bromides. As summarized in Table 2, various 8-alkenyl caffeine derivatives were obtained with mono-, di-, or trisubstituted alkenyl bromides **2**. Although alkenyl bromides are sterically bulky, all of them afforded moderate to good yields. (*Z*)-Bromopropene (**2b**) gave coupling product **3c** in a moderate 42% yield as a single (*E*) isomer (Table 2, Entry 3). Reaction with α-substituted or α,β-disubstituted alkenyl bromides **2c** or **2d** gave **3d** or **3e** in 53 or 85% yield, respectively, revealing a low influence of the substituent position on alkenyl bromides on the outcome of the coupling process (Table 2, Entries 4 and 5). In addition, the reactivity of various α/β-substituted bromostyrenes **2f**–**i** was evaluated in the direct alkenylation with **1a** to give compounds **3g**–**j** in moderate to good yields (Table 2, Entries 7–10). One can note that compound **3i** may be regarded as an analog of isocombretastatin A-4 (*iso*CA-4), a highly promising cytotoxic and antitubulin agent developed in our group.[13]

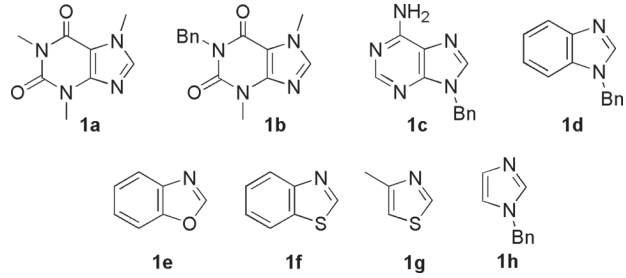
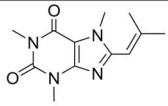
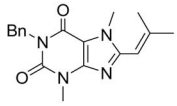
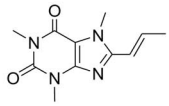
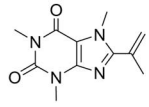
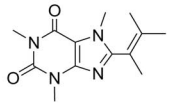
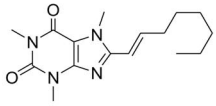
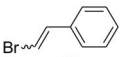
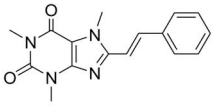
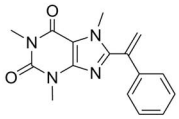
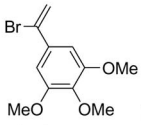
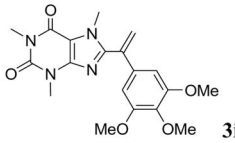
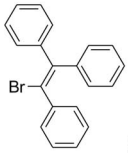
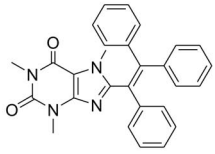


Figure 1. Heterocycles used in this study.

Subsequently, to further expand the scope of our methodology, we used this new catalytic system in the direct C–H alkenylation of other azole heterocycles (Table 3). Overall, we were pleased with the generality of our methodology. The reaction proceeded regioselectively in satisfactory yields with adenine **1c** to afford the corresponding 8-alken-

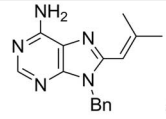
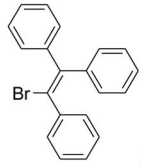
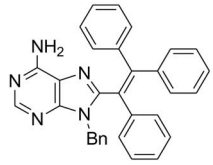
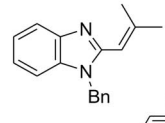
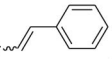
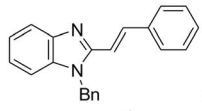
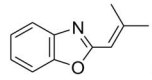
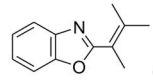
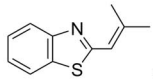
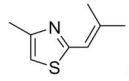
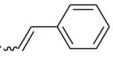
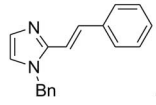
Table 2. Direct alkenylation of caffeine (**1a**) with alkenyl halides.[a]

Entry	1	RX	Product	Yield [%][b]
1	**1a**	 **2a**	 **3a**	87
2	**1b**	 **2a**	 **3b**	82
3	**1a**	 **2b**	 **3c**	42
4	**1a**	 **2c**	 **3d**	53
5	**1a**	 **2d**	 **3e**	85
6	**1a**	 **2e**	 **3f**	55[d,e]
7	**1a**	 **2f**[c]	 **3g**	60
8	**1a**	 **2g**	 **3h**	48
9	**1a**	 **2h**	 **3i**	40
10	**1a**	 **2i**	 **3j**	88[d]

[a] Substrate **1** (1 equiv.), vinyl halide **2** (1.2 equiv.), $Pd(acac)_2$ (2.5 mol-%), CuI (5 mol-%), P(*o*-tolyl)$_3$ (5 mol-%), *t*BuOLi (2 equiv.), THF (0.2 M), 130 °C, (time: see Experimental Section). [b] Isolated yield. [c] Used as a 85:15 *E*/*Z* ratio. [d] Reaction was performed in dioxane at 160 °C for 4 h. [e] Isolated as a pure (*E*) isomer.

yladenines **4a** and **4b** (Table 3, Entries 1 and 2). Noteworthy for this substrate, the reaction was performed in NMP by using a stoichiometric amount of copper iodide for total completion. It was found that the presence of a free NH_2 group at the C6 position was tolerated and may be useful for selective C–N bond-forming reactions to access 6,8,9-trisubstitued purines of biological interest.[14] *N*-Benzyl benzimidazole (**1d**) also underwent clean C2 alkenylation and provided the desired coupling products **4c** and **4d** in excellent yields (Table 3, Entries 3 and 4). 1,3-Benzoxazole (**1e**; Table 3, Entries 5 and 6) and 1,3-benzothiazole (**1f**; Table 3, Entry 7) were found to be suitable substrates, although in the last case a stoichiometric amount of copper iodide and a higher reaction temperature (160 °C) were required to obtain total conversion.

Table 3. Direct alkenylation of heterocycles **1c**–**i** with alkenyl bromides.[a]

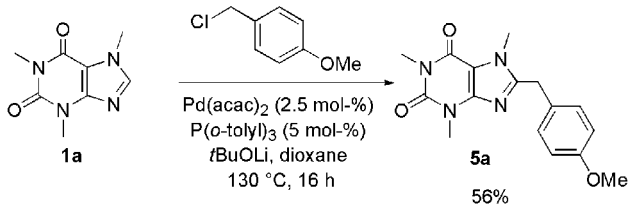
Entry	1	RBr	Product	Yield [%][b]
1	**1c**	 **2a**	 **4a**	66[c]
2	**1c**	 **2i**	 **4b**	54[c]
3	**1d**	 **2a**	 **4c**	83
4	**1d**	 **2f**[f]	 **4d**	82
5	**1e**	 **2a**	 **4e**	65[d]
6	**1e**	 **2d**	 **4f**	51[d]
7	**1f**	 **2a**	 **4g**	52[e]
8	**1g**	 **2a**	 **4h**	63
9	**1h**	 **2f**[f]	 **4i**	0

[a] Substrate **1** (1 equiv.), vinyl halide **2** (1.2 equiv.), $Pd(acac)_2$ (2.5 mol-%), CuI (5 mol-%), P(*o*-tolyl)$_3$ (5 mol-%), *t*BuOLi (2 equiv.), THF (0.2 M), 130 °C, (time: see Experimental Section). [b] Isolated yield. [c] Reaction was performed in NMP using CuI (1 equiv.). [d] Reaction was performed without CuI. [e] Reaction was performed in dioxane at 160 °C using CuI (1 equiv.). [f] Used as a 85:15 *E*/*Z* ratio.

Remarkably, 4-methylthiazole (**1g**) was regioselectively vinylated at the C2 position to furnish **4h** in a good yield (Table 3, Entry 8). However, compounds with higher pK_a value (≥30)[15] such as imidazole **1h** failed and the starting material was recovered unchanged (Table 3, Entry 9).

This optimized protocol was subsequently used to examine the direct coupling reaction of caffeine (**1a**) with *p*-

methoxybenzyl chloride.[4,16] A preliminary experiment, depicted below, showed that *p*-methoxybenzyl chloride reacted with **1a** under our optimized conditions to give coupling product **5a**. It should be mentioned that it was not necessary to add copper iodide as a co-catalyst to obtain a satisfactory 56% yield (Scheme 1), despite the fact that the reaction conditions had never been optimized. To the best of our knowledge, this is the first example of the palladium-catalyzed direct benzylation of caffeine, which provides novel access to a library of C8 benzylcaffeines related to PU3 as hsp90 inhibitors.[17]



Scheme 1. Pd-catalyzed direct benzylation of caffeine (**1a**) with *p*-methoxybenzyl chloride.

Conclusions

In summary, we have developed a highly efficient and versatile Pd/Cu-catalyzed C–H alkenylation reaction of a wide range of heterocycles, including caffeine, adenine, benzimidazole, benzoxazole, benzothiazole and thiazole. The substrate scope of the reaction turned out to be very broad to include not only azoles but also a variety of mono-, di- or trisubstituted alkenyl bromides. This procedure offers an important advance in the direct C–H alkenylation to provide various alkenylheterocycles. In addition, the first reported example of Pd-catalyzed direct benzylation of caffeine has been described. We believe that this methodology should find broad applications in synthetic organic chemistry and pharmaceutical sciences.

Experimental Section

General Procedure for Direct Alkenylation of Caffeine A flame-dried resealable 2–5-mL Pyrex reaction vessel was charged with the solid reactant(s): $Pd(acac)_2$ (2.5 mol-%), CuI (5 mol-%), P(*o*-tolyl)$_3$ (5 mol-%), heterocycle **1** (1 mmol), alkenyl bromide (1.2 mmol), and *t*BuOLi (2 mmol). The reaction vessel was capped with a rubber septum, evacuated, and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and THF (5 mL per mmol) were added through the septum. The septum was replaced with a Teflon screw cap. The reaction vessel was sealed, and then heated at 130 °C (time: see the Experimental Section). The resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with ethyl acetate, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Compound 3a: Reaction time: 2 h. Yield: 87% (216 mg); white solid; m.p. 193–195 °C. TLC: R_f = 0.39 (*c*-hexane/EtOAc, 5/5). IR (neat): $\tilde{\nu}$ = 2944, 2918, 1693, 1655, 1545, 1435, 1368, 1340, 1288, 1225, 1076, 1038, 978, 845, 758, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.02 (br. s, 1 H), 3.90 (s, 3 H), 3.57 (s, 3 H), 3.39 (s, 3 H), 2.22 (s, 3 H), 2.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 151.7, 150.0, 149.1, 148.0, 109.6, 106.3, 31.5, 29.6, 27.8, 27.6, 20.6 ppm. MS (ES+): *m*/*z* = 249 [M + H]$^+$. $C_{12}H_{16}N_4O_2$ (248.13): calcd. C 58.05, H 6.50, N 22.57; found C 57.89, H 6.33, N 22.32.

Compound 3b: Reaction time: 2 h. Yield: 82% (266 mg); white solid; m.p. 173–175 °C. TLC: R_f = 0.55 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2972, 2911, 2877, 2359, 1696, 1654, 1603, 1543, 1479, 1433, 1397, 1342, 1225, 1122, 1073, 922, 831, 758, 748, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (m, 2 H), 7.28 (m, 3 H), 6.02 (s, 1 H), 5.20 (s, 2 H), 3.91 (s, 3 H), 3.57 (s, 3 H), 2.22 (s, 3 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 151.8, 150.4, 149.4, 148.4, 137.7, 128.9 (2 C), 128.5 (2 C), 127.5, 109.8, 106.6, 44.5, 31.8, 29.8, 27.7, 20.8 ppm. MS (ES+): *m*/*z* = 325 [M + H]$^+$. $C_{18}H_{20}N_4O_2$ (324.16): calcd. C 66.65, H 6.21, N 17.27; found C 66.39, H 6.02, N 17.06.

Compound 3c: Reaction time: 2 h. Yield: 42% (98 mg); beige solid; m.p. 190–192 °C. TLC: R_f = 0.34 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2951, 2920, 1695, 1648, 1544, 1488, 1426, 1394, 1315, 1294, 1222, 1040, 969, 933, 743 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (dq, *J* = 15.3, 7.0 Hz, 1 H), 6.31 (dq, *J* = 15.4, 1.6 Hz, 1 H), 3.94 (s, 3 H), 3.56 (s, 3 H), 3.38 (s, 3 H), 1.99 (dd, *J* = 6.9, 1.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 151.7, 150.0, 148.4, 138.0, 115.5, 107.3, 31.4, 29.6, 27.8, 18.9 ppm. MS (ES+): *m*/*z* = 235 [M + H]$^+$. $C_{11}H_{14}N_4O_2$ (234.11): calcd. C 56.40, H 6.02, N 23.92; found C 56.22, H 5.87, N 23.84.

Compound 3d: Reaction time: 4 h. Yield: 53% (124 mg); white solid; m.p. 144–146 °C. TLC: R_f = 0.34 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2958, 2929, 1694, 1653, 1537, 1491, 1432, 1366, 1339, 1287, 1251, 1216, 1123, 1043, 975, 937, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61 (br. s, 1 H), 5.39 (br. s, 1 H), 4.00 (s, 3 H), 3.55 (s, 3 H), 3.38 (s, 3 H), 2.18 (br. s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 155.5, 151.6, 147.7, 133.5, 120.9, 108.0, 33.8, 29.6, 27.9, 22.1 ppm. MS (ES+): *m*/*z* = 235 [M + H]$^+$. $C_{11}H_{14}N_4O_2$ (234.11): calcd. C 56.40, H 6.02, N 23.92; found C 56.19, H 5.69, N 23.78.

Compound 3e: Reaction time: 2 h. Yield: 85% (223 mg); white solid; m.p. 162–164 °C. TLC: R_f = 0.28 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2917, 1709, 1661, 1539, 1486, 1418, 1365, 1342, 1288, 1222, 1132, 1076, 1038, 979, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 3.55 (s, 3 H), 3.37 (s, 3 H), 1.92 (s, 3 H), 1.85 (s, 3 H), 1.55 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 154.8, 151.7, 148.1, 138.9, 117.8, 106.9, 32.2, 29.7, 27.8, 22.3, 20.1, 18.1 ppm. MS (ES+): *m*/*z* = 263 [M + H]$^+$. $C_{13}H_{18}N_4O_2$ (262.14): calcd. C 59.53, H 6.92, N 21.36; found C 59.45, H 6.81, N 21.17.

Compound 3f: Reaction time: 2 h. Yield: 55% (167 mg); beige solid; m.p. 88–90 °C. TLC: R_f = 0.46 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2952, 2927, 2857, 2362, 1700, 1650, 1600, 1546, 1434, 1339, 1290, 1227, 1041, 967, 919, 744, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (dt, *J* = 15.3, 7.1 Hz, 1 H), 6.27 (dt, *J* = 15.4, 1.5 Hz, 1 H), 3.94 (s, 3 H), 3.56 (s, 3 H), 3.37 (s, 3 H), 2.30 (qd, *J* = 7.4, 1.4 Hz, 2 H), 1.51 (m, 2 H), 1.30 (m, 6 H), 0.88 (t, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 151.8, 150.2, 148.5, 143.3, 114.2, 107.5, 33.5, 31.8, 31.5, 29.8, 29.1, 28.7, 28.0, 22.7, 14.2 ppm. MS (ES+): *m*/*z* = 305 [M + H]$^+$. $C_{16}H_{24}N_4O_2$ (304.19): calcd. C 63.13, H 7.95, N 18.41; found C 63.01, H 7.83, N 18.26.

Compound 3g: Reaction time: 2 h. Yield: 60% (178 mg); light-brown solid; m.p. 219–221 °C. TLC: R_f = 0.52 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2953, 2924, 2862, 2361, 1692, 1662, 1598, 1545,

1476, 1447, 1426, 1305, 1288, 1226, 1035, 967, 908, 845, 757, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 15.8 Hz, 1 H), 7.55 (m, 2 H), 7.37 (m, 3 H), 6.87 (d, J = 15.8 Hz, 1 H), 4.02 (s, 3 H), 3.59 (s, 3 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 151.7, 149.9, 148.5, 138.3, 135.5, 129.6, 129.0 (2 C), 127.4 (2 C), 111.2, 107.9, 31.6, 29.8, 28.0 ppm. MS (ES+): m/z = 297 [M + H]$^+$. $C_{16}H_{16}N_4O_2$ (296.13): calcd. C 64.85, H 5.44, N 18.91; found C 64.58, H 5.33, N 18.69.

Compound 3h: Reaction time: 2 h. Yield: 48% (142 mg); beige solid; m.p. 139–141 °C. TLC: R_f = 0.42 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2956, 2908, 1693, 1656, 1601, 1537, 1499, 1433, 1370, 1336, 1286, 1252, 1218, 1033, 976, 936, 920, 743, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.3 (m, 3 H), 7.22 (m, 2 H), 5.99 (s, 1 H), 5.73 (s, 1 H), 3.57 (s, 3 H), 3.56 (s, 3 H), 3.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 151.9, 151.6, 148.0, 137.8, 137.1, 128.9 (3 C), 126.5 (2 C), 122.5, 108.3, 33.4, 29.8, 27.9 ppm. MS (ES+): m/z = 297 [M + H]$^+$. $C_{16}H_{16}N_4O_2$ (296.13): calcd. C 64.62, H 5.23, N 18.51; found C 64.85, H 5.44, N 18.91.

Compound 3i: Reaction time: 2 h. Yield: 40% (155 mg); beige solid; m.p. 207–209 °C. TLC: R_f = 0.42 (*c*-hexane/EtOAc, 2:8). IR (neat): $\tilde{\nu}$ = 3002, 2945, 2922, 2838, 1704, 1651, 1584, 1538, 1510, 1433, 1413, 1370, 1323, 1287, 1251, 1230, 1185, 1124, 1036, 1006, 978, 947, 840 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.48 (s, 2 H), 5.97 (s, 1 H), 5.76 (s, 1 H), 3.85 (s, 3 H), 3.81 (s, 6 H), 3.67 (s, 3 H), 3.61 (s, 3 H), 3.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 153.5 (2 C), 151.7, 151.6, 147.9, 138.8, 137.8, 132.9, 122.2 108.3, 104.0 (2 C), 60.9, 56.2 (2 C), 33.4, 29.8, 27.9 ppm. MS (ES+): m/z = 287 [M + H]$^+$. $C_{19}H_{22}N_4O_5$ (386.16): calcd. C 59.06, H 5.74, N 14.50; found C 58.79, H 5.67, N 14.36.

Compound 3j: Reaction time: 4 h at 160 °C. Yield: 88% (395 mg); yellow solid; m.p. 229–231 °C. TLC: R_f = 0.29 (*c*-hexane/EtOAc, 7:3). IR (neat): $\tilde{\nu}$ = 2953, 2361, 2146, 1689, 1651, 1604, 1540, 1490, 1442, 1424, 1374, 1343, 1288, 1221, 1074, 1041, 1025, 978, 750, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (m, 15 H), 3.56 (s, 3 H), 3.47 (s, 3 H), 3.39 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 153.4, 151.6, 149.2, 148.2, 141.9, 140.8, 138.9, 131.0 (2 C), 130.0 (2 C), 129.5 (2 C), 128.2 (5 C), 128.0 (2 C), 127.9, 127.5, 127.1, 106.7, 32.5, 29.8, 27.9 ppm. MS (ES+): m/z = 449 [M + H]$^+$. $C_{28}H_{24}N_4O_2$ (448.19): calcd. C 74.98, H 5.39, N 12.49; found C 74.83, H 5.11, N 12.16.

Compound 4a: Reaction time: 2 h. Yield: 66% (184 mg); white solid; m.p. 205–207 °C. TLC: R_f = 0.25 (CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3316, 3146, 2937, 2911, 2358, 2336, 1657, 1601, 1571, 1498, 1453, 1430, 1370, 1324, 1295, 1170, 1074, 1032, 979, 943, 889, 829, 727, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.5 (br. s, 1 H), 7.24 (m, 7 H), 6.32 (s, 1 H), 5.39 (s, 2 H), 2.25 (s, 3 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.6, 147.6, 146.2, 137.0, 128.5 (2 C), 127.3, 126.6 (2 C), 110.9, 44.4, 26.9, 20.4 ppm. MS (ES+): m/z = 280 [M + H]$^+$. $C_{16}H_{17}N_5$ (279.15): calcd. C 68.79, H 6.13, N 25.07; found C 68.56, H 6.03, N 24.97.

Compound 4b: Reaction time: 4 h at 160 °C). Yield: 54% (259 mg); beige solid; m.p. 231–233 °C. TLC: R_f = 0.28 (CH_2Cl_2/MeOH, 95:5). IR (neat): $\tilde{\nu}$ = 3310, 3140, 3061, 2364, 2218, 2176, 1638, 1596, 1573, 1494, 1455, 1449, 1369, 1327, 1298, 1077, 1029, 907, 760, 727, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (s, 1 H), 7.10 (m, 16 H), 6.75 (d, J = 7.7 Hz, 2 H), 6.63 (d, J = 7.7 Hz, 2 H), 5.82 (s, 2 H), 4.80 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.95, 152.70 (2 C), 152.33, 150.78, 147.83, 141.97, 141.43, 139.52, 136.59, 131.20 (2 C), 130.44 (2 C), 129.83 (2 C), 128.87, 128.70 (2 C), 128.17 (3 C), 128.04 (4 C), 127.98 (3 C), 127.70, 127.33, 45.92 ppm. MS (ES+): m/z = 480 [M + H]$^+$. $C_{32}H_{25}N_5$ (479.21): calcd. C 80.14, H 5.25, N 14.60; found C 80.01, H 5.02, N 14.33.

Compound 4c: Reaction time: 2 h. Yield: 83% (217 mg); beige solid; m.p. 95–97 °C. TLC: R_f = 0.48 (*c*-hexane/EtOAc, 5:5). IR (neat): $\tilde{\nu}$ = 2926, 2906, 1649, 1601, 1494, 1451, 1397, 1366, 1324, 1283, 1232, 1177, 1001, 922, 841, 745, 727, 693 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (m, 1 H), 7.24 (m, 6 H), 7.03 (m, 2 H), 6.15 (m, 1 H), 5.32 (s, 2 H), 2.25 (s, 3 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.3, 143.2, 136.2, 134.5 128.9 (2 C), 127.7, 126.2 (2 C), 122.4, 122.1, 119.4, 111.4, 109.4, 44.4, 48.9, 27.1, 20.8 ppm. MS (ES+): m/z = 263 [M + H]$^+$. $C_{18}H_{18}N_2$ (262.15): calcd. C 82.41, H 6.92, N 10.68; found C 82.19, H 6.81, N 10.41.

Compound 4d: Reaction time: 2 h. Yield: 82% (255 mg); beige solid; m.p. 177–179 °C. TLC: R_f = 0.55 (*c*-hexane/EtOAc, 7:3). IR (neat): $\tilde{\nu}$ = 2357, 1630, 1493, 1447, 1409, 1368, 1329, 1207, 1071, 981, 929, 756, 731, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, J = 15.8 Hz, 1 H), 7.83 (d, J = 7.8 Hz, 1 H), 7.53 (m, 2 H), 7.30 (m, 9 H), 7.13 (m, 2 H), 7.04 (d, J = 15.8 Hz, 1 H), 5.44 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 143.1, 137.5, 136.0, 135.8, 135.5, 129.0 (3 C), 128.7 (2 C), 127.9, 127.2 (2 C), 126.1 (2 C), 122.8 (2 C), 119.3, 112.9, 109.6, 46.8 ppm. MS (ES+): m/z = 311 [M + H]$^+$. $C_{22}H_{18}N_2$ (310.15): calcd. C 85.13, H 5.85, N 9.03; found C 84.93, H 5.78, N 8.91.

Compound 4e: Reaction time: 2 h. Yield: 65% (113 mg); brown solid; m.p. 58–60 °C. TLC: R_f = 0.47 (*c*-hexane/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 2985, 2922, 2862, 2357, 1650, 1600, 1546, 1452, 1355, 1248, 1134, 1058, 1001, 948, 841, 745 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 1 H), 7.40 (m, 1 H), 7.21 (m, 2 H), 6.19 (m, 1 H), 2.29 (s, 3 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 150.6, 149.7, 141.9, 124.2, 124.1, 119.6, 111.9, 110.1, 27.6, 21.0 ppm. MS (ES+): m/z = 174 [M + H]$^+$. $C_{11}H_{11}NO$ (173.08): calcd. C 76.28, H 6.40, N 8.09; found C 76.03, H 6.19, N 7.92.

Compound 4f: Reaction time: 2 h. Yield: 51% (96 mg); light-brown solid; m.p. 58–60 °C. TLC: R_f = 0.49 (*c*-hexane/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 2983, 2923, 2854, 2362, 1633, 1530, 1454, 1376, 1275, 1177, 1058, 1003, 919, 847, 763 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (m, 1 H), 7.50 (m, 1 H), 7.22 (m, 2 H), 2.26 (s, 3 H), 2.19 (s, 3 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 149.9, 142.8, 141.6, 124.4, 124.0, 119.6, 117.5, 110.2, 23.4, 23.0, 16.8 ppm. MS (ES+): m/z = 188 [M + H]$^+$. $C_{12}H_{13}NO$ (187.10): calcd. C 76.98, H 7.00, N 7.48; found C 76.79, H 6.69, N 7.24.

Compound 4g: Reaction time: 4 h. Yield: 52% (98 mg); brown solid; m.p. 79–81 °C. TLC: R_f = 0.56 (*c*-hexane/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 3050, 2903, 2854, 2357, 2338, 1650, 1540, 1434, 1367, 1316, 1241, 1222, 1157, 1124, 1070, 1015, 887, 839, 756, 724, 638 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.9 Hz, 1 H), 7.84 (d, J = 7.9 Hz, 1 H), 7.45 (t, J = 7.2 Hz, 1 H), 7.33 (t, J = 7.2 Hz, 1 H), 6.61 (s, 1 H), 2.27 (s, 3 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 153.2, 146.0, 134.7, 126.0, 124.6, 122.7, 121.2, 119.6, 27.8, 20.9 ppm. MS (ES+): m/z = 190 [M + H]$^+$. $C_{11}H_{11}NS$ (189.06): calcd. C 69.80, H 5.86, N 7.40; found C 69.62, H 5.71, N 7.39.

Compound 4h: Reaction time: 2 h. Yield: 63% (97 mg); orange oil. TLC: R_f = 0.47 (*c*-hexane/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 2976, 2924, 2856, 2357, 1688, 1647, 1516, 1442, 1374, 1306, 1237, 1109, 1043, 977, 863 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (s, 1 H), 6.52 (s, 1 H), 2.43 (s, 3 H), 2.10 (s, 3 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.1, 152.3, 141.7, 119.6, 112.3, 27.4, 20.5, 17.0 ppm. MS (ES+): m/z = 154 [M + H]$^+$. $C_8H_{11}NS$ (153.06): calcd. C 62.70, H 7.24, N 9.14; found C 62.61, H 7.19, N 9.03.

Compound 5a: Reaction time: 16 h. Yield: 56% (176 mg); white solid; m.p. 172–174 °C. TLC: R_f = 0.5 (EtOAc). IR (neat): $\tilde{\nu}$ = 2961,

2938, 2842, 2362, 1697, 1649, 1543, 1512, 1445, 1427, 1289, 1243, 1218, 1179, 1025, 976, 855 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 4.07 (s, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.57 (s, 3 H), 3.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 155.2, 152.5, 151.6, 147.8, 129.2 (2 C), 126.9, 114.3 (2 C), 107.7, 55.2, 32.6, 31.9, 29.7, 27.8 ppm. MS (ES+): m/z = 313 $[M + H]^+$. $C_{16}H_{18}N_4O_3$ (314.14): calcd. C 61.13, H 5.77, N 17.82; found C 61.02, H 5.69, N 17.79.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra for all new compounds.

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