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Platinum-Catalyzed Michael Addition and Cyclization of Tertiary Amines with Nitroolefins by Dehydrogenation of α,β-sp^3 C−H Bonds

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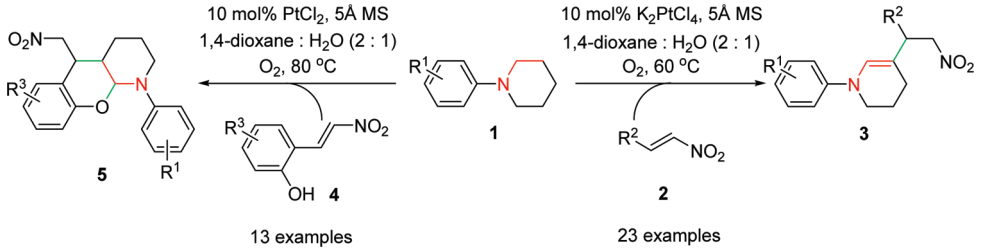
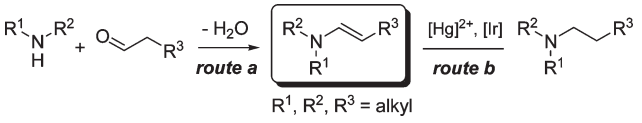


A mild platinum-catalyzed oxidative dehydrogenation of α,β-C(sp^3)−H bonds of tertiary amines in the presence of ambient oxygen is revealed, and the in situ formed enamines subsequently reacting with various nitroolefins resulted in the development of two one-pot synthetic protocols involving Michael addition−elimination and Michael addition−cyclization. By using different functionalized nitroolefins compatible with the current oxidative conditions, two types of structurally divergent products, trisubstituted enamines and chromano[2,3-*b*]piperidines, could be expediently accessed, respectively.

Introduction

Michael addition is one of the most fundamental carbon−carbon bond forming reactions in organic chemistry, wherein enolates or stabilized carbanions are among the nucleophiles usually used for such a case.[1,2] Enamines as enolate equivalents are employed extensively for the selective formation of C−C and C−N bonds in the Michael addition and Diels−Alder reaction, as well as a wide range of other reactions.[3] In the synthetic chemistry of enamines, the condensation between an amine and a carbonyl compound constitutes the classical method for the formation of enamines (route a of Scheme 1),[3] in which acidic, basic, and/or azeotropic conditions are usually required. As an alternative synthetic route, enamines can also be generated from dehydrogenation of tertiary amines mediated by transition metals as reported by Goldman, Henbest, Wickberg, and co-workers (route b of Scheme 1).[4] However, these methods are frequently restricted to relatively harsh reaction conditions.

SCHEME 1. General Strategies for Enamine Formation



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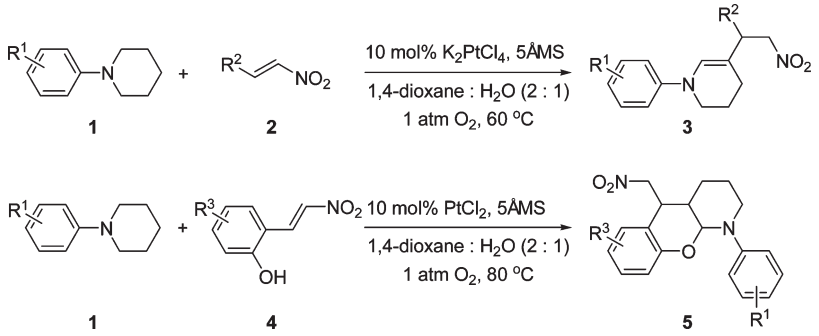
SCHEME 2. Platinum-Catalyzed Reaction of Tertiary Amines with Nitroolefins



Thus, a mild method for the straightforward synthesis of enamines is still of high demand in modern organic synthesis.

Recently, the activation of the hydrogen located at the α-position of the nitrogen atom represents a useful method for the construction of complex molecules.[5] Of them, the cross-dehydrogenative coupling (CDC) constitutes one of such important synthetic transformations involving α C−H oxidative activation of tertiary amines.[6−11] Murahashi,[6] Doyle,[7] Li,[8] and others[9] have developed this kind of oxidative coupling reaction via transition metal catalysis in the presence of oxidants. Beyond these interesting results, Todd and we recently disclosed a metal-free CDC protocol using DDQ[10] and hypervalent iodine(III) reagents[11] as oxidants, respectively. However, simultaneous activation of both α and β hydrogens of an amine nitrogen atom is rarely reported for the generation of enamines. In this relevant area of research, there are two preceding examples, which were recently reported by Weng, Wang, and co-workers,[12,13] demonstrating the in situ formation of enamine intermediates via α,β-dehydrogenation of tertiary amines, but the expected C−H bond activation depends significantly on the use of tertiary aliphatic amines as well as on the use of stoichiometric amounts of diethyl azodicarboxylate (DEAD) or $FeCl_3$.

Our group is persistently interested in the oxidation of tertiary amines to prepare various functionalized heterocyclic compounds. During the course of the study of platinum-catalyzed tandem reactions,[14] we interestingly discovered that tertiary amines could react with nitroolefins in the presence of oxygen under platinum catalysis (Scheme 2), in which two one-pot synthetic protocols involving Michael addition−elimination and Michael addition−cyclization were developed on the basis of the reaction of the in situ generated enamines with different functionalized nitroolefins. To our knowledge, this mild synthesis of enamine intermediates provides a pathway in one-pot manner to the synthetically useful trisubstituted enamines and chromano-[2,3-*b*]piperidines, which have received increased attention due to their medicinal potentials, especially as antiallergic and antiulcer drugs.[15] Herein we report our results for the synthesis of a series of functionalized substituted enamines and chromano[2,3-*b*]piperidines from readily available simple starting materials.

Results and Discussion

Michael Addition−Elimination. Our study began with the reaction of 1.0 equiv of *N*-phenylpiperidine (**1a**), 1.5 equiv of (*E*)-2-nitrostyrene (**2a**), and 0.1 equiv of $PtCl_2$ as catalyst, and 1,4-dioxane/H_2O (2:1) as solvent at 80 °C. To our delight, the desired trisubstituted enamine **3a** as a solid was isolated in 26% yield (entry 1 of Table 1). Addition of hexafluoroisopropanol (HFIP) as a weak Brønsted acid increased the reaction yield to about 50% (entries 2−3). To improve the reaction efficiency, the effect of acids was then investigated. It was found that the weakly acidic 5 Å molecular sieves (MS) as additive gave the best result (entry 4), whereas strong acids were less active or ineffective (entries 5−7). In addition to $PtCl_2$, other platinum catalysts were also

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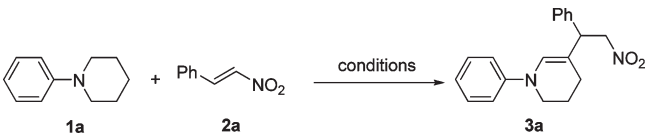
TABLE 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	catalyst (mol %)	conditions[b]	yield (%)
1	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 80 °C	26
2	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 1 equiv HFIP, 80 °C	50
3	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 2 equiv HFIP, 80 °C	52
4	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 80 °C	57
5	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 2equiv HOAc, 80 °C	40
6	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 2 equiv HBF_4, 80 °C	trace
7	$PtCl_2$ (10)	1, 4-dioxane/H_2O (2:1) 2 equiv $HSbF_6$, 80 °C	trace
8	$PtCl_4$ (10)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 80 °C	58
9	K_2PtCl_4 (10)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 80 °C	65
10	$PtCl_2$ (10), COD (20)	1, 4-dioxane/H_2O (2:1) 80 °C	trace
11	$PtCl_2$ (10), CO (1 atm)	1, 4-dioxane/H_2O (2:1) 80 °C	trace
12	K_2PtCl_4 (10)	DME/H_2O (2:1) 5 Å MS, 80 °C	39
13	K_2PtCl_4 (10)	THF/H_2O (2:1) 5 Å MS, 80 °C	30
14	K_2PtCl_4 (10)	DMF/H_2O (2:1) 5 Å MS, 80 °C	45
15	K_2PtCl_4 (10)	H_2O, 5 Å MS, 80 °C	21
16	K_2PtCl_4 (10)	1, 4-dioxane/H_2O (2.5:1) 5 Å MS, 80 °C	52
17	K_2PtCl_4 (10)	1, 4-dioxane/H_2O (1.5:1) 5 Å MS, 80 °C	42
18	K_2PtCl_4 (10)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 60 °C, O_2	70
19	K_2PtCl_4 (2.5)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 60 °C, O_2	36
20	K_2PtCl_4 (5)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 60 °C, O_2	60
21	K_2PtCl_4 (15)	1, 4-dioxane/H_2O (2:1) 5 Å MS, 60 °C, O_2	45
22	-	1, 4-dioxane/H_2O (2:1) 5 Å MS, 60 °C, O_2	0

[a]All reactions were carried out by using *N*-phenylpiperidine (0.2 mmol), (*E*)-2-nitrostyrene (0.3 mmol), catalyst (0.02 mmol), and solvent (2 mL) for 14 h. [b]HFIP = hexafluoroisopropanol; MS = molecular sieves.

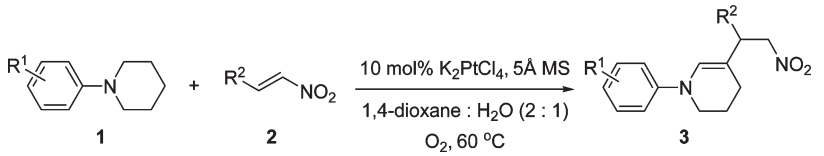
tested in this reaction (entries 8−11). Among the platinum catalytic systems examined, K_2PtCl_4 as catalyst delivered the desired product **3a** with the improved yield of 65% (entry 9), demonstrating the fact that only hypervalent platinum catalysts could activate α-hydrogen of the nitrogen atom in this case. With an attempt to optimize the yield of the product, we further studied the influence of different reaction media (entries 12−14). From the results obtained, it can be seen that 1,4-dioxane/H_2O was the best solvent of choice (entry 9), and the reaction media investigated (e.g., DME/H_2O, THF/H_2O, DMF/H_2O, and H_2O) gave **3a** only in 21−45% yields (entries 12−15). It should be noted that the best ratio of 1,4-dioxane/H_2O was 2:1, and the yields of **3a** were lowered when the ratio of water was either increased or decreased (entries 16 and 17). Moreover, the effect of oxygen as oxidant was also examined, and it was interestingly found that a higher yield of 70% could be obtained even at lower temperature under oxygen atmosphere (entry 18), clearly demonstrating that oxygen can speed up this oxidative transformation of tertiary amines. Furthermore, the catalyst loading was investigated (entries 19−21). Lowering the catalyst loading led to a slow conversion with the decreased yield of **3a** (entries 19 and 20), and even no expected product was observed in the absence of platinum catalyst (entry 22). Surprisingly, increasing the amount of catalyst to 15 mol % gave the considerably decreased yield of 45% (entry 21). With the series of detailed investigations mentioned above, the reaction conditions were eventually optimized (entry 18): 10 mol % of K_2PtCl_4 as catalyst, 1,4-dioxane/H_2O (2:1) as mixed solvent, 5 Å molecular sieves as additive, at 60 °C, and under oxygen atmosphere.

Having established the optimal reaction conditions, we next explored the scope of the reaction. This reaction was successfully extended to a series of substituted *N*-aryl piperidines and nitroolefins. The corresponding results are listed in Table 2. Under the optimized conditions, *N*-phenyl piperidine reacted with various substituted (*E*)-nitrostyrenes, providing **3a**−**h** in 40−70% yields (Table 2, entries 1−8). From these results, it can be seen that this reaction tolerated a variety of functional groups at the ortho, meta, and para positions of the phenyl moiety in substituted (*E*)-nitrostyrenes, indicating that the steric effect had little impact on this one-pot transformation. Nevertheless, a relatively lower yield was obtained while using the aromatic nitroolefin with a strongly electron-donating substituent in the phenyl ring (enrty 8), which could be ascribed to the fact that the electron-donating substituent decreased the electrophilic reactivity of nitroolefin. The nitroolefin possessing a heterocyclic ring, such as furan nucleus, can also participate in this reaction to give the desired product **3i** in 41% yield (entry 9). Noteworthily, the substrate scope of the present platinum-catalyzed Michael addition−elimination reaction can be further extended to the aliphatic nitroolefin albeit in very low yield (entry 10).

The property of the substituent on the aryl group of *N*-aryl piperidines also influences the yield of the product. From entries 11−17 of Table 2, it can be seen that an electron-donating substituent at the *N*-aryl piperidine favors product formation (entries 11−14), while an electron-withdrawing group (e.g., Cl and Br) slightly hinders the reaction (entries 15−17). This might be due to the fact that the electron-donating substituent increases the nucleophilic oxidative reactivity of tertiary amines. The reaction of *N*-aryl piperidine possessing a benzyl group at the 2-position with (*E*)-nitrostyrene **2a**, as shown in eq 1 of Scheme 3, proceeded smoothly to give the product **3u** in a lower yield even at slightly elevated temperature. Additionally, the size of the ring of cyclic tertiary amine was also tested. *N*-Phenylazepane exhibited a lower reactivity to form **3v** (20% yield, eq 2 of Scheme 3) and *N*-phenyl pyrrolidine did not undergo the expected reaction. It is worth mentioning that *N*-aryl morpholine could also participate in this reaction although a lower yield was obtained (eq 3 of Scheme 3).

Michael Addition−Cyclization. During the course of the study of the mechanism of aforementioned Michael addition−elimination, we envisioned that the enamine **A** reacted with electrophiles $\mathbf{E}^+$ (e.g., nitroolefins) to form putative

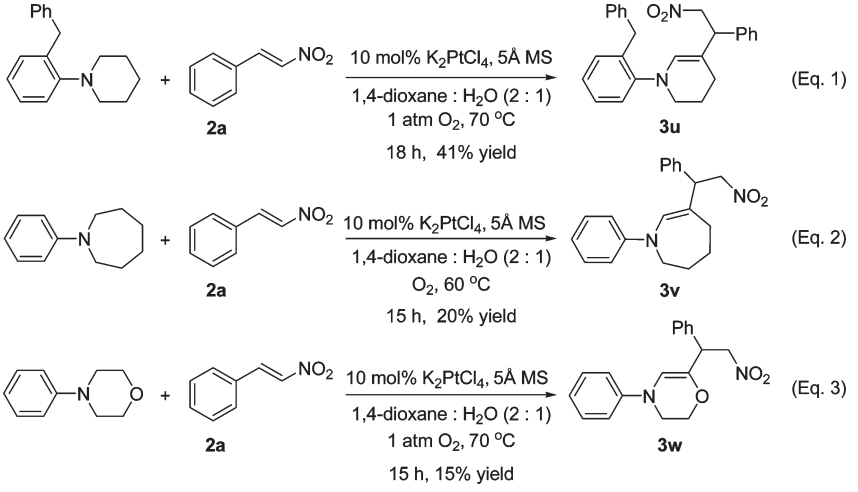
TABLE 2. Platinum-Catalyzed Michael Addition−Elimination of *N*-Aryl Piperidines with Nitroolefins[a]



entry	R^1	R^2	product	time (h)	yield (%)
1	H	phenyl	**3a**	13	70
2	H	4-methylphenyl	**3b**	14	65
3	H	3-methylphenyl	**3c**	16	61
4	H	2-methylphenyl	**3d**	14	46
5	H	4-chlorophenyl	**3e**	16	56
6	H	3-chlorophenyl	**3f**	19	54
7	H	2-chlorophenyl	**3g**	16	67
8	H	4-methoxyphenyl	**3h**	14	40
9	H	2-furyl	**3i**	14	41
10	H	cyclohexyl	**3j**	21	20[b]
11	4-methyl	phenyl	**3k**	15	55
12	3-methyl	phenyl	**3l**	14	58
13	4-methoxyl	phenyl	**3m**	15	71
14	3,4-dimethyl	phenyl	**3n**	15	52
15	4-chloro	phenyl	**3o**	15	43
16	3-chloro	phenyl	**3p**	14	32
17	4-bromo	phenyl	**3q**	15	40
18	4-methyl	4-chlorophenyl	**3r**	14	61
19	4-methyl	2-chlorophenyl	**3s**	14	68
20	4-methyl	4-methylphenyl	**3t**	14	47

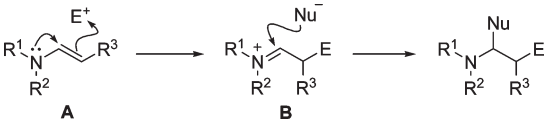
[a]All reactions were carried out by using **1** (0.2 mmol), nitroolefins **2** (0.3 mmol), K_2PtCl_4 (0.02 mmol), 1, 4-dioxane/H_2O (2:1, 2 mL), and 5 Å molecular sieves (50 mg) at 60 °C under oxygen atmosphere. [b]The reaction was carried out at 80 °C.

SCHEME 3. Platinum-Catalyzed Michael Addition Reaction



intermediary iminium ion **B**, which can be readily trapped by nucleophiles (Scheme 4).[16] Phenol is one of the nucleophiles that often is used for this purpose. To further explore the scope of the reaction involving the in situ formation of enamines, we extended our study to the substituted nitrovinylphenols **4** instead of simple aromatic nitroolefins **2** used in Michael addition−elimination sequence. As described in Table 3, a variety of chromano[2,3-*b*]piperidine derivatives were produced smoothly in the presence of catalytic amounts of $PtCl_2$ in 1,4-dioxane/H_2O (2:1) at

SCHEME 4. Michael Addition−Cyclization



80 °C under 1 atm of O_2, although the longer reaction period and higher temperature were necessary to complete this Michael addition−cyclization initiated by catalytic oxidative dehydrogenation of tertiary amines. From the results of Table 3, it was found that the electronic effects and the positions of the substitutents in **1** did not show

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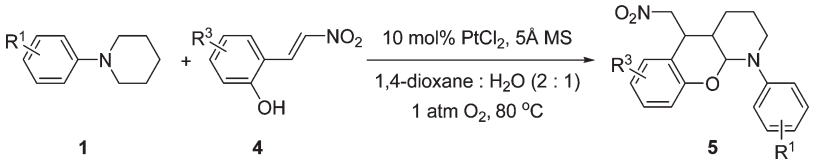
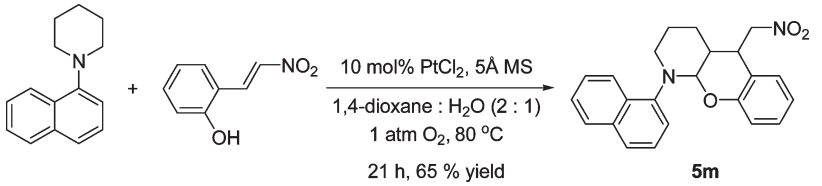
TABLE 3. Platinum-Catalyzed Michael Addition−Cyclization of *N*-Aryl Piperidines with Nitrovinylphenols[a]



entry	R^1	R^3	product	time (h)	yield (%)
1	H	H	**5a**	19	65
2	4-methoxyl	H	**5b**	19	57
3	4-methyl	H	**5c**	22	62
4	4-bromo	H	**5d**	22	52
5	3,4-dimethyl	H	**5e**	19	59
6	3-methyl	H	**5f**	22	52
7	3-chloro	H	**5g**	25	48
8	4-chloro	H	**5h**	22	56
9	2-benzyl	H	**5i**	21	65
10	H	5-methoxyl	**5j**	20	62
11	H	5-methyl	**5k**	21	50
12	H	3-methyl	***5l***	22	29

[a]All reactions were carried out by using **1** (0.3 mmol), **4** (0.2 mmol), $PtCl_2$ (0.02 mmol), 1, 4-dioxane/H_2O (2:1, 2 mL) and 5 Å molecular sieves (50 mg) at 80 °C under oxygen atmosphere.

SCHEME 5. Platinum-Catalyzed Michael Addition−Cyclization



obvious influences on the reaction efficiency. However, when employing the substituted nitrovinylphenol **4** bearing the substituent R^3 ortho to the hydroxyl, the unfavorable steric effect was observed remarkably and the reaction yield is quite low (entry 12). It should be noted that several functional groups such as methoxy, chloro, and bromo were also compatible with this reaction. In addition, *N*-(1-naphthyl)piperidine was also tolerated in this reaction (Scheme 5). To further confirm the structural assignment of products in the present Michael addition−cyclization, the relative configuration of the product **5i** was unambiguously assigned by X-ray crystallography.

Proposed Mechanism. A tentative mechanism for the product formation is proposed in Scheme 6. Analogous to pathways for the oxidation of tertiary amines by electrochemical process,[17] metals,[18] and oxidants,[10,11] the intermediate iminium ion **C** is formed in the presence of platinum catalyst, oxygen, and water. First, the platinum catalyst [Pt] coordinates to the nitrogen and then goes through the activation of C (sp^3)−H adjacent to the nitrogen in the presence of oxygen, affording an iminium ion intermediate **C**.[19] Second, the subsequent β-hydrogen elimination in **C** produces the enamine **D**, which undergoes Michael addition with nitroolefins **2a** and **4a** to give the Michael adduct intermediates **E** (path A) and **F** (path B), respectively. By further hydrogen elimination in iminium ion moiety of **E**, the trisubstituted enamine product **3a** could be delivered readily. Contrarily, the iminium ion moiety in **F** was intramolecularly attacked by the nucleophilic hydroxyl group, smoothly giving the structurally different product **5a**.[20]

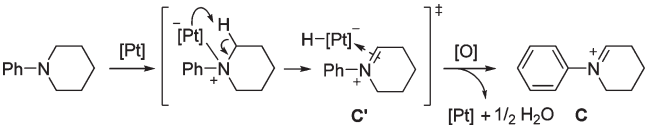
Conclusions

In conclusion, a mild platinum-catalyzed dehydrogenation of α,β-sp^3 C−H bonds adjacent to the nitrogen of tertiary amines was successfully established, and the in situ formed enamines initially serving as carbon-nucleophiles reacted with various nitroolefins, leading to the development of two one-pot protocols involving Michael

(17) (a) Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. *J. Org. Chem.* **1987**, *52*, 536. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, 206. (c) Shono, T. *Tetrahedron* **1984**, *40*, 811. (d) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. (e) Weinberg, N. L.; Brown, E. A. *J. Org. Chem.* **1966**, *31*, 4058.

(18) (a) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (b) Han, G.; LaPorte, M. G.; McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 9483.

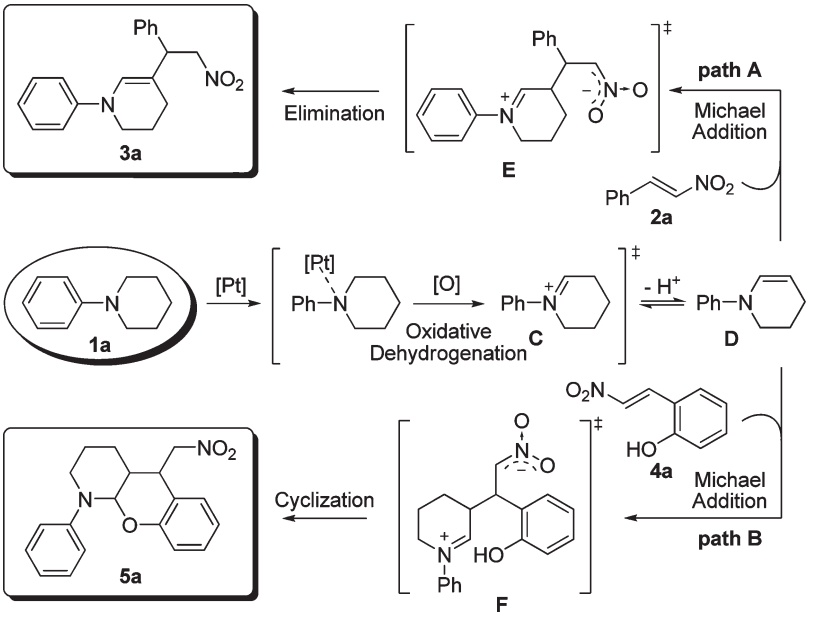
(19) As for the plausible process concerning the generation of iminium ion **C**, please see the scheme below.



The platinum catalyst first coordinated to the nitrogen atom, followed by insertion into the α C−H bond, leading to an iminium ion coordinated to a platinum metal hydride **C′** (see: Anguille, S.; Brunet, J.-J.; Chu, N.-C.; Diallo, O.; Pages, C.; Vincendeau, S. *Organometallics* **2006**, *25*, 2943). The platinum hydride was then oxidized by oxygen to regenerate the platinum catalyst with release of water (see: Chen, L.; Davies, J. A. *Inorg. Chim. Acta* **1990**, *175*, 41).

(20) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580.

SCHEME 6. Proposed Mechanism



addition−elimination and Michael addition−cyclization. This platinum-catalyzed reaction provided an effective access to structurally divergent heterocyclic compounds. Additionally, the present reaction can tolerate a large number of substrates, including aromatic and aliphatic nitroolefins as Michael acceptors as well as various functionalized (*E*)-nitrovinylphenols as Michael acceptors/donors with significant structural variation.

Experimental Section

General Procedure for the Preparation of 5-(2-Nitro-1-aryl-ethyl)-1-aryl-1,2,3,4-tetrahydropyridine, 3a−w. To a Schlenk tube were added *N*-phenyl piperidine (0.20 mmol), K_2PtCl_4 (8.3 mg, 10 mol %), 2-nitrovinylbenzene (0.30 mmol), and powdered 5 Å molecular sieves (50 mg). The Schlenk tube was purged under vacuum and then refilled with oxygen 3 times. A mixed solvent of 1,4-dioxane/H_2O (2:1, 2.0 mL) was added by syringe, and then the mixture was stirred at 60 °C. When the reaction was considered complete as determined by TLC analysis, ethyl acetate (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The residue was purified by flash chromatography on alkalescence silica gel to afford the corresponding products.

3a was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 48.5 mg (70%) of the indicated compound as a solid after 13 h: mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.35 (m, 2 H), 7.21−7.28 (m, 5 H), 6.84−6.87 (m, 3 H), 6.56 (s, 1 H), 4.83−4.88 (m, 1 H), 4.71−4.75 (m, 1 H), 4.16−4.20 (m, 1 H), 3.41−3.44 (m, 2 H), 1.96−2.05 (m, 1 H), 1.84−1.91 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 138.8, 129.2, 128.8, 127.4, 127.3, 119.7, 115.2, 109.4, 77.9, 49.3, 45.1, 22.5, 22.2; IR (neat, cm^{-1}) 3056, 2924, 2848, 1950, 1709, 1657, 1596, 1551, 1497, 1377, 1340, 1319, 1263, 1200, 1162, 1080, 1030, 996, 877, 738, 700, 659, 615, 528; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{20}N_2O_2$ (M + H) 309.1598, found 309.1595.

3b was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 57.2 mg (65%) of the indicated compound as a solid after 14 h: mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.28 (m, 2 H), 7.09−7.14 (m, 4 H), 6.83−6.87 (m, 3 H), 6.55 (s, 1 H), 4.81−4.86 (m, 1 H), 4.68−4.73 (m, 1 H), 4.12−4.16 (m, 1 H), 3.40−3.43 (m, 2 H), 2.32 (s, 3 H), 1.95−2.04 (m, 1 H), 1.83−1.91 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 136.9, 135.8, 129.4, 129.2, 127.2, 127.1, 119.6, 115.1, 109.6, 78.1, 48.9, 45.1, 22.5, 22.2, 20.9; IR (neat, cm^{-1}) 3027, 2923, 2845, 1733, 1657, 1597, 1551, 1499, 1376, 1319, 1261, 1200, 1163, 995, 875, 816, 752, 695, 658, 520; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}N_2O_2$ (M + H) 323.1754, found 323.1748.

3c was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 46.1 mg (61%) of the indicated compound as an oil after 16 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.28 (m, 3 H), 7.00−7.08 (m, 3 H), 6.83−6.87 (m, 3 H), 6.56 (s, 1 H), 4.82−4.88 (m, 1 H), 4.69−4.73 (m, 1 H), 4.12−4.16 (m, 1 H), 3.41−3.43 (m, 2 H), 2.33 (s, 3 H), 1.84−2.05 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 138.7, 138.4, 129.2, 128.6, 128.2, 128.1, 127.1, 124.3, 119.7, 115.1, 109.5, 77.9, 49.3, 45.1, 22.5, 22.2, 21.4; IR (neat, cm^{-1}) 3033, 2923, 2844, 1733, 1657, 1597, 1551, 1498, 1377, 1319, 1261, 1199, 1171, 995, 873, 788, 751, 698, 662, 523; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}N_2O_2$ (M + H) 323.1754, found 323.1761.

3d was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 31.0 mg (46%) of the indicated compound as an oil after 14 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.23 (m, 5 H), 7.10−7.13 (m, 1 H), 6.81−6.87 (m, 3 H), 6.49 (s, 1 H), 4.83−4.89 (m, 1 H), 4.66−4.71 (m, 1 H), 4.39−4.44 (m, 1 H), 3.37−3.48 (m, 2 H), 2.40 (s, 3 H), 1.81−2.04 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 136.6, 136.5, 131.1, 129.2, 127.8, 127.1, 126.1, 125.7, 119.7, 115.1, 108.3, 77.8, 45.1, 22.8, 22.3, 19.5; IR (neat, cm^{-1}) 3063, 2927, 2842, 1924, 1734, 1655, 1597, 1550, 1498, 1376, 1319, 1262, 1161, 1036, 995, 909, 875, 753, 694, 658, 619, 571, 523; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}N_2O_2$ (M + H) 323.1754, found 323.1757.

3e was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 40.8 mg (56%) of the indicated compound as a solid after 16 h: mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.23−7.31 (m, 4 H), 7.15−7.17 (m, 2 H), 6.85−6.88 (m, 3 H), 6.54 (s, 1 H), 4.79−4.85 (m, 1 H), 4.68−4.72 (m, 1 H), 4.14−4.18 (m, 1 H), 3.42−3.43 (m, 2 H), 1.82−1.99 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 137.4, 133.2, 129.2, 128.9, 128.7, 127.6, 119.9, 115.2, 108.8, 77.7, 48.6, 45.1, 22.6, 22.2; IR (neat, cm^{-1}) 3062, 2926, 2844, 1732, 1656, 1597, 1551, 1496, 1376, 1340, 1319, 1262, 1200, 1163, 1090, 1013, 995, 875, 752, 694, 660, 570, 532; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_2$ (M + H) 343.1208, found 343.1201.

3f was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 28.2 mg (54%) of the indicated compound as a solid after 19 h: mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.29 (m, 5 H), 7.10−7.13 (m, 1 H), 6.86−6.89 (m, 3 H), 6.56 (s, 1 H), 4.81−4.86 (m, 1 H), 4.69−4.74 (m, 1 H), 4.14−4.18 (m, 1 H), 3.43−3.45 (m, 2 H), 1.82−2.01 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 141.0, 134.6, 130.0, 129.2, 127.7, 127.6, 125.5, 119.9, 115.3, 108.5, 77.6, 48.9, 45.1, 22.4, 22.1; IR (neat, cm^{-1}) 3062, 2926, 2843, 1939, 1709, 1656, 1596, 1551, 1498, 1376, 1340, 1319, 1262, 1199, 1165, 1081, 996, 878, 787, 752, 696, 662, 566, 525; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_2$ (M + H) 343.1208, found 343.1202.

3g was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 51.8 mg (67%) of the indicated compound as a solid after 16 h: mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.41 (m, 1 H), 7.18−7.28 (m, 5 H), 6.83−6.87 (m, 3 H), 6.58 (s, 1 H), 4.70−4.85 (m, 3 H), 3.43−3.46 (m, 2 H), 1.88−2.05 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 136.0, 134.4, 130.3, 129.2, 128.5, 128.3, 127.7, 126.9, 119.8, 115.3, 107.3, 76.7, 45.3, 45.2, 23.1, 22.2; IR (neat, cm^{-1}) 3463, 2984, 2938, 1888, 1740, 1597, 1554, 1466, 1444, 1374, 1242, 1098, 1047, 1001, 937, 918, 847, 786, 756, 694, 634, 608; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_2$ (M + H) 343.1208, found 343.1213.

3h was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 25 mg (40%) of the indicated compound as a solid after 14 h: mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.28 (m, 2 H), 7.13−7.15 (m, 2 H), 6.85−6.87 (m, 5 H), 6.53 (s, 1 H), 4.80−4.85 (m, 1 H), 4.67−4.72 (m, 1 H), 4.11−4.15 (m, 1 H), 3.78 (s, 3 H), 3.43 (br, 2 H), 1.86−2.04 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 146.6, 130.7, 129.2, 128.5, 127.0, 119.7, 115.1, 114.1, 109.8, 78.2, 55.2, 48.6, 45.1, 22.7, 22.2; IR (neat, cm^{-1}) 3102, 3034, 2931, 2839, 1731, 1657, 1600, 1550, 1509, 1462, 1377, 1337, 1315, 1256, 1200, 1176, 1115, 1031, 994, 971, 830, 753, 695, 658, 587, 523; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_3$ (M + H) 339.1703, found 339.1709.

3i was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 28 mg (41%) of the indicated compound as an oil after 14 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.36 (m, 1 H), 7.24−7.27 (m, 2 H), 6.85−6.87 (m, 3 H), 6.57 (s, 1 H), 6.32−6.33 (m, 1 H), 6.12−6.13 (m, 1 H), 4.70−4.84 (m, 2 H), 4.25−4.29 (m, 1 H), 3.45−3.48 (m, 2 H), 1.91−2.15 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 146.5, 142.0, 129.2, 128.9, 119.9, 115.3, 110.4, 106.5, 106.3, 76.5, 45.1, 43.9, 22.2, 21.9; IR (neat, cm^{-1}) 3062, 2926, 2846, 1711, 1659, 1597, 1552, 1499, 1377, 1321, 1262, 1200, 1167, 1078, 1013, 996, 972, 915, 879, 813, 749, 695, 597, 524; HRMS (ESI) m/z calcd for $C_{17}H_{18}N_2O_3$ (M + H) 299.1390, found 299.1382.

3j was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 17 mg (20%) of the indicated compound as an oil after 21 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.25 (m, 2 H), 6.82−6.84 (m, 3 H), 6.35 (s, 1 H), 4.58−4.62 (m, 1 H), 4.37−4.43 (m, 1 H), 3.45 (br, 2 H), 2.49−2.56 (m, 1 H), 2.06−2.12 (m, 1 H), 1.92−1.93 (m, 3 H), 1.67−1.76 (m, 6 H), 1.34−1.42 (m, 1 H), 1.14−1.26 (m, 3 H), 0.95−1.07 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 129.1, 128.6, 119.4, 115.0, 107.6, 77.8, 51.0, 45.3, 37.5, 31.5, 31.0, 30.9, 26.2, 26.1, 22.3, 20.7; IR (neat, cm^{-1}) 3034, 2926, 2850, 1713, 1658, 1597, 1549, 1499, 1445, 1379, 1325, 1260, 1194, 1165, 995, 869, 750, 693, 661, 576, 522; HRMS (ESI) m/z calcd for $C_{19}H_{26}N_2O_2$ (M + H) 315.2067, found 315.2062.

3k was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 36.5 mg (55%) of the indicated compound as a solid after 15 h: mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.34 (m, 2 H), 7.21−7.27 (m, 3 H), 7.05−7.07 (m, 2 H), 6.75−6.77 (m, 2 H), 6.51 (s, 1 H), 4.82−4.87 (m, 1 H), 4.70−4.75 (m, 1 H), 4.15−4.19 (m, 1 H), 3.36−3.43 (m, 2 H), 2.27 (s, 3 H), 1.84−2.03 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.9, 129.7, 129.1, 128.7, 127.7, 127.4, 127.3, 115.4, 108.6, 77.9, 49.3, 45.4, 22.5, 22.2, 20.4; IR (neat, cm^{-1}) 3061, 3028, 2983, 2930, 2848, 1885, 1738, 1657, 1614, 1571, 1553, 1516, 1448, 1375, 1320, 1243, 1203, 1163, 1046, 937, 847, 810, 702, 635, 607, 528; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_2$ (M + H) 323.1754, found 323.1752.

3l was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 35.8 mg (58%) of the indicated compound as a solid after 14 h: mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.35 (m, 2 H), 7.21−7.27 (m, 3 H), 7.13−7.17 (m, 1 H), 6.66−6.69 (m, 3 H), 6.56 (s, 1 H), 4.84−4.89 (m, 1 H), 4.72−4.76 (m, 1 H), 4.16−4.20 (m, 1 H), 3.41−3.43 (m, 2 H), 2.33 (s, 3 H), 1.83−2.04 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 139.0, 138.9, 129.0, 128.7, 127.5, 127.4, 127.3, 120.7, 115.9, 112.4, 109.1, 77.9, 49.3, 45.1, 22.5, 22.2, 21.7; IR (neat, cm^{-1}) 3030, 2923, 2845, 1711, 1656, 1601, 1551, 1494, 1448, 1377, 1348, 1318, 1262, 1199, 1161, 1080, 1027, 997, 771, 698, 659, 615, 561, 529; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_2$ (M + H) 323.1754, found 323.1750.

3m was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 47 mg (71%) of the indicated compound as a solid after 15 h: mp 84−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.34 (m, 2 H), 7.21−7.27 (m, 3 H), 6.79−6.82 (m, 4 H), 6.44 (s, 1 H), 4.83−4.88 (m, 1 H), 4.70−4.75 (m, 1 H), 4.14−4.18 (m, 1 H), 3.76 (s, 3 H), 3.33−3.42 (m, 2 H), 1.82−2.03 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 141.2, 138.9, 128.7, 128.3, 127.4, 127.3, 117.2, 114.6, 108.1, 77.9, 55.6, 49.3, 46.0, 22.4, 22.2; IR (neat, cm^{-1}) 3027, 2927, 2836, 1711, 1651, 1615, 1577, 1546, 1509, 1428, 1373, 1323, 1262, 1238, 1178, 1033, 988, 817, 745, 699, 638, 549, 525; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_3$ (M + H) 339.1703, found 339.1708.

3n was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 32 mg (52%) of the indicated compound as an oil after 15 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.34 (m, 2 H), 7.21−7.27 (m, 3 H), 7.00−7.02 (m, 1 H), 6.67−6.68 (m, 1 H), 6.59−6.63 (m, 1 H), 6.52 (s, 1 H), 4.83−4.88 (m, 1 H), 4.71−4.76 (m, 1 H), 4.15−4.19 (m, 1 H), 3.37−3.40 (m, 2 H), 2.24 (s, 3 H), 2.18 (s, 3 H), 1.84−2.04 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.0, 137.3, 130.2, 128.7, 128.0, 127.9, 127.4, 127.3, 116.9, 112.9, 108.4, 78.0, 49.3, 45.4, 22.5, 22.2, 20.1, 18.7; IR (neat, cm^{-1}) 3026, 2923, 2857, 1877, 1734, 1656, 1610, 1551, 1505, 1450, 1376, 1320, 1262, 1201, 1180, 1045, 996, 852, 807, 761, 701, 642, 608, 586, 527; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2O_2$ (M + H) 337.1911, found 337.1909.

3o was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 30.5 mg (43%) of the indicated compound as a solid after 15 h: mp 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.35 (m, 2 H), 7.19−7.29 (m, 5 H), 6.75−6.78 (m, 2 H), 6.49 (s, 1 H), 4.84−4.89 (m, 1 H), 4.71−4.76 (m, 1 H), 4.16−4.20 (m, 1 H), 3.34−3.43 (m, 2 H), 1.83−2.05 (m, 4 H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 145.1, 138.6, 129.0, 128.8, 127.4, 127.3, 126.9, 124.6, 116.2, 110.3, 77.9, 49.3, 45.2, 22.3, 22.1; IR (neat, cm^{-1}) 3029, 2924, 2844, 1657, 1593, 1550, 1495, 1450, 1377, 1346, 1320, 1261, 1199, 1163, 1095, 975, 816, 762, 700, 627, 520; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_2$ (M + H) 343.1208, found 343.1215.

3p was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 20 mg (32%) of the indicated compound as a solid after 14 h: mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.36 (m, 6 H), 6.81−6.83 (m, 2 H), 6.71−6.74 (m, 1 H), 6.53 (s, 1 H), 4.85−4.91 (m, 1 H), 4.73−4.78 (m, 1 H), 4.17−4.21 (m, 1 H), 3.39−3.42 (m, 2 H), 1.88−2.06 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 138.6, 135.0, 130.2, 128.8, 127.5, 127.4, 126.6, 119.5, 115.0, 113.0, 110.9, 77.8, 49.3, 45.1, 22.4, 22.1; IR (neat, cm^{-1}) 3028, 2923, 2850, 1656, 1591, 1550, 1486, 1439, 1377, 1321, 1259, 1199, 1101, 990, 844, 765, 700, 653, 615, 551; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_2$ (M + H) 343.1208, found 343.1202.

3q was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 26.5 mg (40%) of the indicated compound as a solid after 15 h: mp 64−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.35 (m, 4 H), 7.21−7.29 (m, 3 H), 6.70−6.73 (m, 2 H), 6.49 (s, 1 H), 4.84−4.89 (m, 1 H), 4.71−4.76 (m, 1 H), 4.16−4.20 (m, 1 H), 3.38−3.39 (m, 2 H), 1.85−2.05 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 138.6, 131.9, 128.8, 127.5, 127.4, 126.7, 116.7, 111.9, 110.4, 77.9, 49.3, 45.1, 22.4, 22.1; IR (neat, cm^{-1}) 3029, 2952, 2924, 2854, 1710, 1660, 1588, 1551, 1493, 1453, 1377, 1319, 1261, 1198, 1164, 1076, 1002, 816, 761, 701, 678, 623, 525; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrN_2O_2$ (M + H) 387.0703, found 387.0708.

3r was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 52.8 mg (61%) of the indicated compound as a solid after 14 h: mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.31 (m, 2 H), 7.13−7.17 (m, 3 H), 6.66−6.71 (m, 3 H), 6.54 (s, 1 H), 4.79−4.85 (m, 1 H), 4.68−4.73 (m, 1 H), 4.13−4.17 (m, 1 H), 3.40−3.45 (m, 2 H), 2.33 (s, 3 H), 1.80−1.98 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 139.0, 137.5, 133.1, 129.1, 128.9, 128.7, 127.7, 120.9, 116.0, 112.4, 108.6, 77.8, 48.6, 45.1, 22.5, 22.1, 21.7; IR (neat, cm^{-1}) 3029, 2923, 2843, 1711, 1656, 1613, 1551, 1515, 1491, 1439, 1376, 1320, 1261, 1200, 1164, 1091, 1013, 978, 885, 811, 736, 717, 662, 630, 536; HRMS (ESI) m/z calcd for $C_{20}H_{21}ClN_2O_2$ (M + H) 357.1364, found 357.1370.

3s was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 47.1 mg (68%) of the indicated compound as a solid after 14 h: mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.41 (m, 1 H), 7.18−7.25 (m, 3 H), 7.12−7.16 (m, 1 H), 6.65−6.69 (m, 3 H), 6.58 (s, 1 H), 4.69−4.85 (m, 3 H), 3.42−3.45 (m, 2 H), 2.32 (s, 3 H), 1.86−2.03 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 138.9, 136.0, 134.4, 130.3, 129.0, 128.5, 127.7, 126.9, 120.7, 116.1, 112.5, 107.0, 76.7, 45.3, 45.2, 23.1, 22.2, 21.7; IR (neat, cm^{-1}) 3038, 2923, 2842, 1733, 1711, 1657, 1601, 1584, 1551, 1494, 1376, 1318, 1263, 1199, 1159, 1039, 998, 909, 869, 759, 693, 657, 615, 568, 532; HRMS (ESI) m/z calcd for $C_{20}H_{21}ClN_2O_2$ (M + H) 357.1364, found 357.1381.

3t was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 28.2 mg (47%) of the indicated compound as an oil after 14 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−7.16 (m, 5 H), 6.66−6.69 (m, 3 H), 6.55 (s, 1 H), 4.81−4.87 (m, 1 H), 4.69−4.74 (m, 1 H), 4.12−4.16 (m, 1 H), 3.40−3.43 (m, 2 H), 2.32 (s, 6 H), 1.83−2.04 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 138.9, 136.9, 135.8, 130.1, 129.4, 129.2, 129.0, 127.3, 127.2, 120.6, 115.9, 112.4, 109.4. 78.1, 48.9, 45.2, 22.5, 22.3, 21.7, 20.9; IR (neat, cm^{-1}) 3026, 2922, 2845, 1734, 1656, 1602, 1551, 1495, 1440, 1376, 1318, 1262, 1199, 1159, 1044, 997, 817, 773, 723, 695, 658, 589, 522; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2O_2$ (M + H) 337.1911, found 337.1919.

3u was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 34.0 mg (41%) of the indicated compound as an oil after 18 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.33 (m, 5 H), 7.12−7.17 (m, 7 H), 7.00−7.08 (m, 2 H), 6.00 (s, 1 H), 4.64−4.69 (m, 1 H), 4.52−4.57 (m, 1 H), 3.99−4.05 (m, 3 H), 3.16−3.18 (m, 2 H), 1.72−1.97 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 141.1, 139.3, 135.5, 131.7, 131.5, 128.7, 128.6, 128.3, 127.4, 127.3, 127.2, 125.9, 124.6, 124.5, 107.3, 77.9, 49.0, 48.8, 37.4, 22.6, 22.2; IR (neat, cm^{-1}) 3060, 2923, 2840, 1725, 1655, 1551, 1491, 1450, 1377, 1309, 1258, 1197, 1074, 974, 888, 763, 732, 699, 614, 554; HRMS (ESI) m/z calcd for $C_{26}H_{26}N_2O$ (M + H) 399.2067, found 399.2077.

3v was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 10.5 mg (20%) of the indicated compound as an oil after 15 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.38 (m, 7 H), 6.80−6.83 (m, 3 H), 6.31 (s, 1 H), 4.86−4.91 (m, 1 H), 4.76−4.82 (m, 1 H), 4.23−4.27 (m, 1 H), 3.62−3.75 (m, 2 H), 2.11−2.15 (m, 1 H), 1.99−2.06 (m, 1 H), 1.73−1.79 (m, 2 H), 1.50−1.56 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 138.5, 132.3, 129.3, 128.8, 127.5, 127.4, 123.4, 118.6, 113.7, 77.9, 50.1, 48.1, 28.0, 27.2, 24.0; IR (neat, cm^{-1}) 3029, 2926, 2855, 1733, 1650, 1596, 1551, 1498, 1375, 1341, 1199, 1035, 987, 882, 750, 696, 656, 515; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_2$ (M + H) 323.1754, found 323.1750.

3w was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 9.5 mg (15%) of the indicated compound as an oil after 15 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.36 (m, 5 H), 7.22−7.26 (m, 2 H), 6.76−6.84 (m, 3 H), 5.96 (s, 1 H), 4.96−5.01 (m, 1 H), 4.67−4.72 (m, 1 H), 4.09−4.22 (m, 3 H), 3.49−3.58 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 137.5, 134.2, 129.3, 128.8, 127.7, 127.6, 119.4, 114.1, 108.5, 77.5, 64.7, 47.3, 44.2; IR (neat, cm^{-1}) 3060, 2923, 2865, 1677, 1594, 1552, 1496, 1462, 1386, 1296, 1211, 1080, 1014, 751, 696, 614, 578, 558, 520; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2O_3$ (M + H) 311.1390, found 311.1393.

General Procedure for the Preparation of 5-(Nitromethyl)-1-phenyl-2,3,4,4a,5,10a-hexahydro-1*H*-chromeno[2,3-*b*]pyridine, 5a−m. To a Schlenk tube were added *N*-phenyl piperidine (0.40 mmol), $PtCl_2$ (5.3 mg, 10 mol %), nitrovinylphenol (0.20 mmol), and powdered 5 Å molecular sieves (50 mg). The Schlenk tube was purged under vacuum and then refilled with oxygen 3 times. A mixed solvent of 1,4-dioxane/H_2O (2:1, 2.0 mL) was added by syringe, and then the mixture was stirred at 80 °C. When the reaction was considered complete as determined by TLC analysis, ethyl acetate (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The residue was purified by flash chromatography on alkalescence silica gel to afford corresponding products.

5a was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 42.2 mg (65%) of the indicated compound as a solid after 19 h: mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.32 (m, 2 H), 7.14−7.23 (m, 3 H), 7.09 (d, J = 7.2 Hz, 1 H), 6.97 (t, J = 7.2 Hz, 1 H), 6.89 (t, J = 7.6 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 5.53 (d, J = 2.0 Hz, 1 H), 4.60 (d, J = 7.6 Hz, 2 H), 3.49 (t, J = 15.2 Hz, 1 H), 3.35−3.38 (m, 2 H), 2.15−2.18 (m, 1 H), 1.83−1.89 (m, 2 H), 1.48−1.64 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 150.2, 129.6, 129.1, 121.6, 120.9, 119.0, 117.5, 117.0, 82.8, 80.3, 44.0, 40.9, 35.4, 24.9, 24.1; IR (neat, cm^{-1}) 3062, 2930, 2856, 1940, 1710, 1600, 1583, 1550, 1490,

1454, 1410, 1377, 1300, 1252, 1224, 1170, 1113, 1035, 954, 883, 758, 696, 649, 530; HRMS (ESI) m/z calcd for $C_{19}H_{20}N_2O_3$ (M + H) 325.1547, found 325.1542.

5b was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 42.6 mg (57%) of the indicated compound as a solid after 19 h: mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08−7.19 (m, 4 H), 6.83−6.91 (m, 4 H), 5.38 (d, J = 1.2 Hz, 1 H), 4.59 (d, J = 8.0 Hz, 2 H), 3.78 (s, 3 H), 3.48 (t, J = 7.6 Hz, 1 H), 3.33−3.39 (m, 1 H), 3.18−3.21 (m, 1 H), 2.16−2.18 (m, 1 H), 1.83−1.89 (m, 2 H), 1.43−1.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 154.2, 144.1, 129.5, 129.0, 121.5, 120.9, 117.5, 117.1, 114.3, 83.9, 80.3, 55.5, 44.8, 40.9, 35.5, 25.0, 24.1; IR (neat, cm^{-1}) 3042, 2928, 2858, 2053, 1608, 1583, 1549, 1510, 1441, 1377, 1293, 1246, 1230, 1167, 1112, 1033, 988, 953, 876, 825, 755, 705, 647, 629, 577, 539; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_4$ (M + H) 355.1652, found 355.1651.

5c was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 43.7 mg (62%) of the indicated compound as a solid after 22 h: mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05−7.18 (m, 6 H), 6.87−6.90 (m, 1 H), 6.82−6.84 (m, 1 H), 5.48 (d, J = 1.6 Hz, 1 H), 4.59 (d, J = 8.0 Hz, 2 H), 3.49 (t, J = 7.6 Hz, 1 H), 3.27−3.38 (m, 2 H), 2.30 (s, 3 H), 2.14−2.17 (m, 1 H), 1.82−1.91 (m, 2 H), 1.43−1.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 147.9, 131.1, 129.6, 129.5, 129.0, 120.9, 119.3, 117.5, 117.1, 83.1, 80.3, 44.2, 40.9, 35.4, 24.9, 24.1, 20.5; IR (neat, cm^{-1}) 3028, 2934, 2857, 2737, 1732, 1611, 1582, 1550, 1514, 1487, 1454, 1409, 1377, 1298, 1251, 1225, 1170, 1113, 1069, 1036, 988, 955, 910, 882, 841, 816, 757, 736, 648, 593, 530; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_3$ (M + H) 339.1703, found 339.1707.

5d was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 44 mg (52%) of the indicated compound as a solid after 22 h: mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.40 (m, 2 H), 7.15−7.19 (m, 1 H), 7.09−7.12 (m, 1 H), 6.99−7.03 (m, 2 H), 6.91 (t, J = 7.2 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 5.47 (d, J = 2.0 Hz, 1 H), 4.61 (d, J = 7.2 Hz, 2 H), 3.50 (t, J = 7.6 Hz, 1 H), 3.30−3.34 (m, 2 H), 2.14−2.16 (m, 1 H), 1.82−1.89 (m, 2 H), 1.46−1.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 149.3, 131.9, 129.6, 129.2, 121.2, 120.8, 117.5, 116.9, 114.1, 82.6, 80.3, 44.1, 40.8, 35.3, 24.8, 23.9; IR (neat, cm^{-1}) 3061, 2925, 2843, 1710, 1657, 1588, 1550, 1493, 1451, 1377, 1347, 1319, 1262, 1199, 1163, 1078, 1029, 996, 975, 908, 878, 814, 762, 700, 678, 622, 518; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrN_2O_3$ (M + H) 403.0652, found 403.0657.

5e was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 44.3 mg (59%) of the indicated compound as a solid after 19 h: mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.18 (m, 1 H), 7.05−7.09 (m, 2 H), 6.83−6.94 (m, 4 H), 5.48 (d, J = 1.6 Hz, 1 H), 4.57−4.60 (m, 2 H), 3.48 (t, J = 7.6 Hz, 1 H), 3.28−3.38 (m, 2 H), 2.25 (s, 3 H), 2.20 (s, 3 H), 2.14−2.17 (m, 1 H), 1.81−1.90 (m, 2 H), 1.43−1.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 148.2, 137.1, 130.1, 129.8, 129.5, 129.0, 120.8, 120.7, 117.5, 117.1, 116.7, 83.1, 80.4, 44.1, 40.9, 35.4, 24.9, 24.2, 20.1, 18.9; IR (neat, cm^{-1}) 3407, 3015, 2935, 2857, 2734, 1711, 1611, 1582, 1551, 1505, 1487, 1453, 1412, 1376, 1305, 1255, 1223, 1170, 1114, 1038, 1012, 988, 959, 877, 853, 812, 757, 709, 645, 589, 527; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2O_3$ (M + H) 353.1860, found 353.1854.

5f was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 37.5 mg (52%) of the indicated compound as a solid after 22 h: mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.21 (m, 2 H), 7.10 (d, J = 7.2 Hz, 1 H), 6.95−6.96 (m, 2 H), 6.89 (t, J = 7.2 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 6.80 (d, J = 7.2 Hz, 1 H), 5.52 (br, 1 H), 4.59−4.62 (m, 2 H), 3.50 (t, J = 7.6 Hz, 1 H), 3.31−3.37 (m, 2 H), 2.34 (s, 3 H), 2.14−2.17 (m, 1 H), 1.83−1.88 (m, 2 H), 1.58−1.64 (m, 1 H), 1.45−1.55 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 150.2, 138.8, 129.5, 129.1, 128.9, 122.4, 120.9, 119.7, 117.5, 117.1, 116.1, 82.8, 80.4, 44.0, 40.9, 35.4, 24.9, 24.2, 21.7; IR (neat, cm^{-1}) 3038, 2935, 2856, 2728, 1710, 1604, 1583, 1550, 1488, 1453, 1407, 1376, 1301, 1258, 1223, 1168, 1112, 1037, 989, 959, 911, 877, 778, 757, 697, 649, 580, 529; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_3$ (M + H) 339.1703, found 339.1700.

5g was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 35.7 mg (48%) of the indicated compound as a solid after 25 h: mp 40−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.20 (m, 2 H), 7.10−7.12 (m, 2 H), 6.99−7.02 (m, 1 H), 6.89−6.95 (m, 2 H), 6.84−6.86 (m, 1 H), 5.50 (d, J = 2.4 Hz, 1 H), 4.62 (d, J = 8.0 Hz, 2 H), 3.50 (t, J = 7.6 Hz, 1 H), 3.29−3.27 (m, 2 H), 2.13−2.16 (m, 1 H), 1.81−1.88 (m, 2 H), 1.59−1.65 (m, 1 H), 1.46−1.55 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 151.4, 134.8, 130.0, 129.5, 129.2, 121.4, 121.2, 118.9, 117.5, 117.0, 116.9, 82.3, 80.3, 44.0, 40.8, 35.2, 24.7, 23.9; IR (neat, cm^{-1}) 3070, 2937, 2857, 1793, 1710, 1590, 1550, 1484, 1453, 1409, 1377, 1304, 1252, 1223, 1169, 1111, 1038, 990, 960, 887, 848, 803, 759, 717, 690, 648, 615, 580, 532; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_3$ (M + H) 359.1157, found 359.1162.

5h was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 41.7 mg (56%) of the indicated compound as a solid after 22 h: mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.26 (m, 2 H), 7.15−7.23 (m, 1 H), 7.05−7.11 (m, 3 H), 6.89−6.93 (m, 1 H), 6.82−6.84 (m, 1 H), 5.46 (d, J = 2.0 Hz, 1 H), 4.59−4.62 (m, 2 H), 3.50 (t, J = 7.6 Hz, 1 H), 3.28−3.34 (m, 2 H), 2.14−2.17 (m, 1 H), 1.82−1.89 (m, 2 H), 1.58−1.64 (m, 1 H), 1.45−1.52 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 148.8, 129.5, 129.2, 128.9, 126.6, 121.1, 120.4, 117.4, 116.9, 82.7, 80.3, 44.2, 40.8, 35.3, 24.8, 23.9; IR (neat, cm^{-1}) 3040, 2936, 2857, 1881, 1732, 1586, 1551, 1492, 1454, 1410, 1376, 1300, 1249, 1225, 1169, 1112, 1041, 988, 956, 884, 823, 758, 709, 686, 640, 614, 580, 528; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_2O_3$ (M + H) 359.1157, found 359.1160.

5i was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 54.5 mg (65%) of the indicated compound as a solid after 21 h: mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.68 (m, 1 H), 7.28−7.29 (m, 1 H), 7.21−7.25 (m, 3 H), 7.11−7.18 (m, 5 H), 6.98−7.00 (m, 1 H), 6.81−6.87 (m, 2 H), 4.70 (d, J = 2.0 Hz, 1 H), 4.20−4.25 (m, 1 H), 4.09−4.14 (m, 1 H), 3.98−4.05 (m, 2 H), 3.42−3.49 (m, 1 H), 3.29−3.33 (m, 1 H), 2.71−2.74 (m, 1 H), 1.95−1.99 (m, 1 H), 1.67−1.79 (m, 2 H), 1.38−1.56 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 149.3, 141.6, 136.8, 131.3, 129.5, 128.9, 128.4, 128.3, 127.2, 126.1, 125.8, 125.5, 120.6, 117.4, 117.3, 84.6, 80.1, 45.4, 40.7, 37.6, 35.5, 25.1, 24.1; IR (neat, cm^{-1}) 3025, 2933, 2853, 1735, 1602, 1583, 1551, 1488, 1451, 1405, 1375, 1294, 1226, 1169, 1109, 1046, 988, 956, 879, 841, 759, 733, 698, 649, 610, 558, 512; HRMS (ESI) m/z calcd for $C_{26}H_{26}N_2O$ (M + H) 415.2016, found 415.2018.

5j was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 44 mg (62%) of the indicated compound as a solid after 20 h: mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.6 Hz, 2 H), 7.12−7.14 (m, 2 H), 6.96 (t, J = 7.6 Hz, 1 H), 6.74−6.79 (m, 2 H), 6.61−6.62 (m, 1 H), 5.48 (d, J = 2.0 Hz, 1 H), 4.61 (d, J = 7.6 Hz, 2 H), 3.74 (s, 3 H), 3.46 (t, J = 7.6 Hz, 1 H), 3.34−3.37 (m, 2 H), 2.11−2.15 (m, 1 H), 1.82−1.88 (m, 2 H), 1.49−1.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 150.2, 147.9, 129.1, 121.4, 118.9, 118.3, 117.4, 115.6, 113.5, 82.5, 80.4, 55.7, 44.0, 41.2, 35.4, 24.9, 24.2; IR (neat, cm^{-1}) 3060,

3033, 2997, 2936, 2856, 1732, 1598, 1550, 1496, 1463, 1408, 1377, 1333, 1280, 1220, 1174, 1159, 1102, 1038, 991, 960, 881, 846, 816, 760, 735, 696, 655, 590, 524; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_4$ (M + H) 355.1652, found 355.1650.

5k was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 36.7 mg (50%) of the indicated compound as a solid after 21 h: mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.32 (m, 2 H), 7.13−7.15 (m, 2 H), 6.95−6.99 (m, 2 H), 6.90 (br, 1 H), 6.73−6.75 (m, 1 H), 5.50 (d, J = 2.0 Hz, 1 H), 4.59−4.63 (m, 2 H), 3.45 (t, J = 7.6 Hz, 1 H), 3.35−3.38 (m, 2 H), 2.26 (s, 3 H), 2.12−2.16 (m, 1 H), 1.83−1.89 (m, 2 H), 1.49−1.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.3, 130.2, 129.8, 129.7, 129.1, 121.5, 119.0, 117.3, 116.7, 82.6, 80.4, 44.1, 40.9, 35.5, 24.9, 24.2, 20.4; IR (neat, cm^{-1}) 3393, 2930, 2856, 1732, 1596, 1550, 1495, 1408, 1376, 1223, 1166, 1122, 1039, 990, 958, 880, 818, 759, 695, 648, 583, 527; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_3$ (M + H) 339.1703, found 339.1708.

5l was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 20 mg (29%) of the indicated compound as an oil after 22 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.33 (m, 2 H), 7.19−7.24 (m, 2 H), 6.94−7.05 (m, 3 H), 6.81 (t, J = 7.2 Hz, 1 H), 5.48 (d, J = 1.6 Hz, 1 H), 4.60 (d, J = 7.6 Hz, 2 H), 3.49 (t, J = 7.6 Hz, 1 H), 3.37−3.43 (m, 2 H), 2.16−2.17 (m, 1 H), 2.14 (s, 3 H), 1.83−1.91 (m, 2 H), 1.59−1.63 (m, 1 H), 1.46−1.54 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 150.6, 130.0, 129.0, 127.0, 126.8, 121.8, 120.4, 119.6, 116.4, 82.9, 80.5, 44.6, 41.0, 35.3, 25.0, 24.1, 15.8; IR (neat, cm^{-1}) 3052, 2924, 2853, 1597, 1551, 1496, 1467, 1408, 1376, 1298, 1261, 1223, 1208, 1170, 1132, 1105, 1078, 1030, 989, 943, 906, 881, 809, 758, 739, 697, 651, 557, 524; HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2O_3$ (M + H) 339.1703, found 339.1702.

5m was obtained according to the above procedure. The reaction mixture was chromatographed with 30:1 hexanes/EtOAc to afford 38.4 mg (50%) of the indicated compound as a solid after 21 h: mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.63−7.65 (m, 2 H), 7.51−7.55 (m, 1 H), 7.43−7.48 (m, 2 H), 7.14−7.18 (m, 1 H), 7.06−7.08 (m, 1 H), 6.85−6.89 (m, 2 H), 5.29 (d, J = 1.6 Hz, 1 H), 4.44−4.53 (m, 2 H), 3.57−3.64 (m, 1 H), 3.47−3.51 (m, 1 H), 3.08−3.12 (m, 1 H), 2.36−2.39 (m, 1 H), 1.99−2.11 (m, 1 H), 1.83−1.86 (m, 1 H), 1.54−1.70 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 147.1, 134.6, 129.6, 129.3, 129.0, 128.4, 125.9, 125.7, 124.7, 123.2, 120.8, 119.4, 117.5, 117.1, 84.9, 80.2, 45.6, 41.1, 35.4, 25.2, 24.4; IR (neat, cm^{-1}) 3052, 2934, 2854, 1709, 1580, 1550, 1487, 1455, 1406, 1376, 1337, 1316, 1291, 1261, 1225, 1169, 1111, 1088, 1032, 987, 954, 910, 883, 849, 801, 776, 758, 736, 704, 646, 579, 549, 513; HRMS (ESI) m/z calcd for $C_{23}H_{22}N_2O_3$ (M + H) 375.1703, found 375.1707.

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Supporting Information Available: The detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.