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Rapid Synthesis of CDP840 with 2-Pyrimidyl Vinyl Sulfide as a Platform

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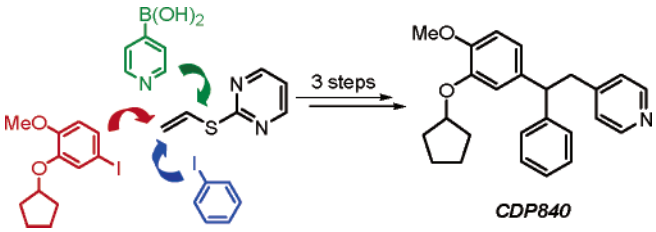


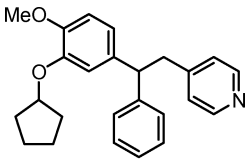
A rapid synthesis of CDP840 (a potential therapeutic agent for asthma), using 2-pyrimidyl vinyl sulfide as a platform, has been established. This method includes a stereoselective double Mizoroki−Heck-type arylation, a Liebeskind−Srogl-type cross-coupling reaction, and a Pd/C-catalyzed hydrogenation.

The synthesis of densely substituted (functionalized) organic structures has been an important subject in organic synthesis. In view of their synthesis as well as potential applications as functional materials and pharmaceuticals, we have been investigating the chemistry (synthesis and properties) of multisubstituted olefins during the last several years. In particular, we have developed a number of syntheses of multisubstituted olefins based on a sequential installation of substituents on a C=C or C≡C core of an appropriate starting material (platform).[1−4]

For example, we have developed a programmable synthesis of triarylethenes through a Pd-catalyzed sequential triarylation using vinyl(2-pyridyl)silane or vinylboronate as a platform.[1,2] From the triarylethene-based extended π-system library, we were able to find a number of interesting fluorescent materials as well as interesting photophysical properties.[1b,c,2] Moreover, we have finally developed a programmable synthesis of tetraarylethenes through a Pd-catalyzed sequential tetraarylation of a vinyl 2-pyrimidyl sulfide platform.[3] As for our application to the synthesis of pharmaceutically important molecules, we established a programmable synthesis of tamoxifen-type tetrasubstituted olefins using alkynyl(2-pyridyl)silane as a platform.[4]

During these investigations toward multisubstituted olefins, we became aware that such olefins should also be excellent precursors for multisubstituted ethane structures by functionalizing the remaining C=C core of multisubstituted olefins (Scheme 1). As functionalizing methods, for example, carbometalation (X = C, Y = M), hydrometalation (H, M), hydrogenation (H, H), and epoxidation (−O−) may be applicable. In this paper, we report on a rapid synthesis of CDP840 (**1**) using 2-pyrimidyl vinyl sulfide as a platform.

CDP840 (**1**), which has an interesting 1,1,2-triarylethane structure, is a potential therapeutic agent for asthma as a selective phosphodiesterase (PDE) IV inhibitor.[5] PDE IV is believed to be the dominant isozyme present in inflammatory cells and airway smooth muscle. Inhibition of PDE IV leads to an increase in the concentration of cyclic GMP, and gives rise to suppression of cellular function in inflammatory cells.



CDP840 (**1**)

Several syntheses of CDP840 including both racemic and asymmetric approaches were reported so far.[6,7] However, they suffered from a relatively long procedure (6−7 steps). We envisaged that the sequence of double Mizoroki−Heck-type arylation and cross-coupling starting from 2-pyrimidyl vinyl sulfide (**2**)[3,8] followed by hydrogenation of the C=C bond would afford CDP840 (**1**) very rapidly (Scheme 2). Such a synthesis would offer an opportunity for diversity-oriented synthesis, which would enable the production and screening of a series of CDP840-type triarylethanes.

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(1) Vinyl(2-pyridyl)silane as a platform: (a) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (b) Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3695. (c) Itami, K.; Ohashi, Y.; Yoshida, J. *J. Org. Chem.* **2005**, *70*, 2778. Also see: (d) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (e) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600.

(2) Vinyl boronate pinacol ester as a platform: Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J. *Org. Lett.* **2004**, *6*, 4093.

(3) Vinyl 2-pyrimidyl sulfide as a platform: Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778.

(4) Alkynyl(2-pyridyl)silane as a platform: (a) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (b) Kamei, T.; Itami, K.; Yoshida, J. *Adv. Synth. Catal.* **2004**, *346*, 1824.

(5) Celltech Therapeutics LTD, U.S. Patent No. 5,608, 070.

(6) Previous syntheses: (a) Celltech Therapeutics LTD, U.S. Patent No. 5,622,977. (b) Houpis, I. N.; Molina, A.; Dorziotis, I.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 7131. (c) Lynch, J. E.; Choi, W.-B.; Churchill, H. R. O.; Volante, R. P.; Reamer, R. A.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 9223. (d) Alexander, R. P.; Warrellow, G. J.; Eaton, M. A. W.; Boyd, E. C.; Head, J. C.; Porter, J. R.; Brown, J. A.; Reuberson, J. T.; Hutchinson, B.; Turner, P.; Boyce, B.; Barnes, D.; Mason, B.; Cannell, A.; Taylor, R. J.; Zomaya, A.; Millican, A.; Leonard, J.; Morphy, R.; Wales, M.; Perry, M.; Allen, R. A.; Gozzard, N.; Hughes, B.; Higgs, G. *Bioorg. Med. Chem.* **2002**, *12*, 1451. (e) Aggarwal, V, K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274.

(7) The configuration of the enantiomer that shows the activity is *R*.[6]

(8) Vinyl sulfide **2** was easily prepared from 2-thiocyanatopyrimidine (derived from 2-mercaptopyrimidine) and vinylmagnesium bromide: (a) Miyashita, A.; Nagasaki, I.; Kawano, A.; Suzuki, Y.; Iwamoto, K.; Higashino, T. *Heterocycles* **1997**, *45*, 745. (b) Nagasaki, I.; Matsumoto, M.; Yamashita, M.; Miyashita, A. *Heterocycles* **1999**, *51*, 1015.

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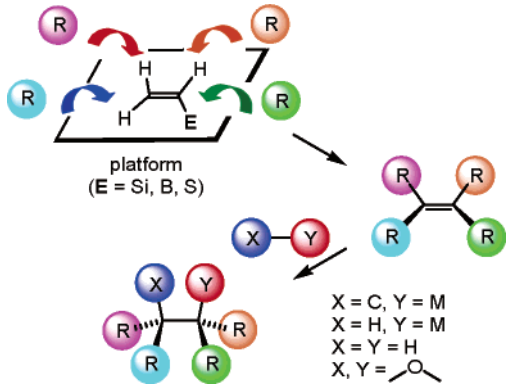
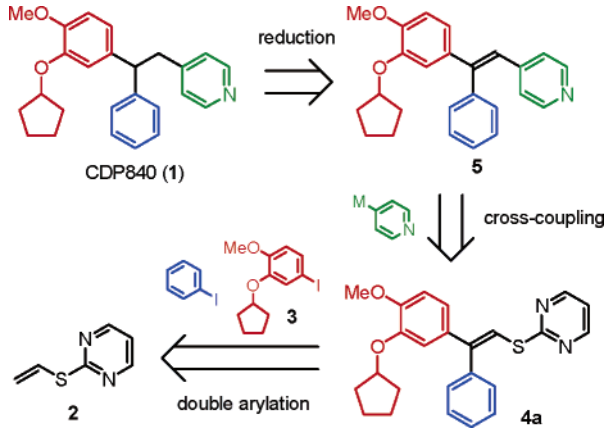
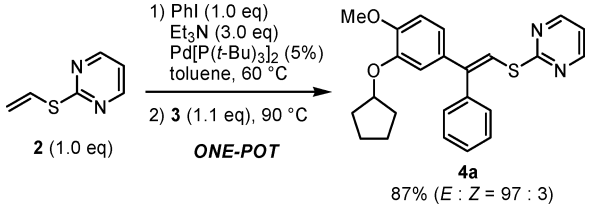
SCHEME 1. Synthetic Strategy for Multisubstituted Ethane Structures through C=C Functionalization of Multisubstituted Olefins



SCHEME 2. Synthetic Strategy for CDP840



SCHEME 3. Stereoselective Synthesis of 4a by the Double Mizoroki–Heck Reaction of 2

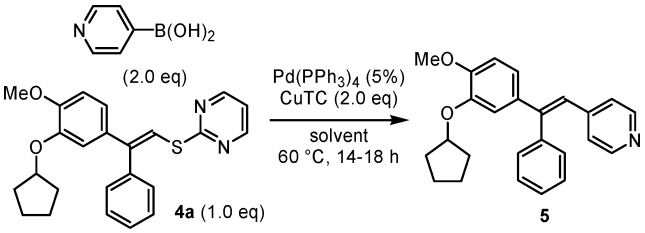


At first, double Mizoroki–Heck-type arylation of 2-pyrimidyl vinyl sulfide (**2**) was investigated (Scheme 3). The stereoselective installation of two aryl groups (phenyl and 3-cyclopentyloxy-4-methoxyphenyl groups) at the β-C–H bonds of **2** was achieved by following the procedure developed previously.[3] Thus, a toluene solution of **2** (1.0 equiv), iodobenzene (1.0 equiv), Et_3N (3.0 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %) was stirred at 60 °C for 4 h to afford monoarylated vinyl sulfide in situ.[9] Thereafter, aryl iodide **3**[10] (1.1 equiv) was added to the solution and the mixture was stirred for an additional 18 h at 90 °C to give the desired β,β-diarylated vinyl sulfide **4a** in 87% isolated yield (Scheme 3). The stereochemistry of **4a** was determined to be 97% *E* as judged by NMR analysis.

(9) Pd/P(*t*-Bu)$_3$ catalyst for Mizoroki–Heck reactions: (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Itami, K.; Yamazaki, D.; Yoshida, J. *Org. Lett.* **2003**, *5*, 2161. (c) References 1b, 1c, 2, and 3.

(10) **3** was prepared in one step from 5-iodo-2-methoxyphenol. See the Supporting Information.

TABLE 1. Optimization of the Liebeskind–Srogl-type Cross-Coupling Reaction of 4a with 4-Pyridylboronic Acid



entry	solvent	**5** (yield, %)	**4a** (recovery, %)
1	THF	19	57
2	EtOH	0	29
3	*t*-BuOH	10	53
4	CH_3CN	9	68
5	DMF	42	37
6	DMA	49	41
7	DMI	57	34
8[a]	DMI	66	23

[a] 3.0 equiv of 4-pyridylboronic acid and CuTC were employed.

With the requisite **4a** in hand, we embarked on the installation of the 4-pyridyl group onto the alkenyl–sulfur bond.[11] According to our previous synthesis of multisubstituted olefins using Pd-catalyzed cross-coupling reactions of alkenyl sulfides with Grignard reagents as a final step,[3] our initial choice was to use 4-pyridylmagnesium chloride as the coupling partner for **4a** in the synthesis of **5**. However, no cross-coupling occurred between **4a** and 4-pyridylmagnesium chloride (3.0 equiv) under our standard conditions (5 mol % Pd[P(*t*-Bu)$_3$]$_2$, 60 °C, toluene)[3] and a considerable amount of **4a** was recovered. This may be partially due to the thermal instability of 4-pyridylmagnesium chloride.[12]

As an alternative to this Pd-catalyzed procedure, we have recently reported the iron-catalyzed cross-coupling reaction of alkenyl sulfides with Grignard reagents.[13] Since this reaction proceeds at room temperature in many cases, we applied this protocol in the installation of the 4-pyridyl group. Unfortunately, however, the reaction of **4a** with 4-pyridylmagnesium chloride (3.0 equiv) under the influence of Fe(acac)$_3$ (5 mol %) in THF at room temperture gave the desired product **5** only in 9% yield (68% recovery of **4a**).

Thus, we turned to the Liebeskind–Srogl-type cross-coupling reaction (an alternative cross-coupling reaction of sulfides with arylboronic acids as coupling partners).[14] When the original conditions reported by Liebeskind (Pd(PPh$_3$)$_4$, CuTC,[15] THF, 60 °C) were applied in the reaction of **4a** with 4-pyridylboronic acid, the cross-coupling product **5** was obtained in 19% yield (Table 1, entry 1). Subsequently we found that the choice of solvent is

(11) A review on metal-catalyzed cross-coupling reactions using sulfides: Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89.

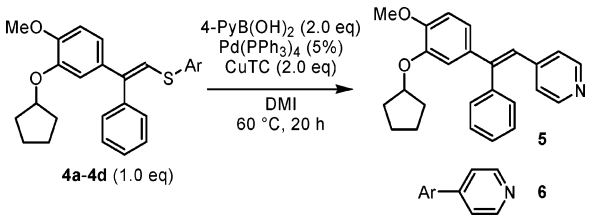
(12) (a) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 5845. (b) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.

(13) Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J. *Org. Lett.* **2005**, *7*, 1219.

(14) (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (b) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (c) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

(15) CuTC = copper(I) thiophene-2-carboxylate. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

TABLE 2. The Effect of Sulfur Substituent in the Liebeskind−Srogl Coupling Reaction



entry	Ar	**5** (%)[a]	**6** (%)[a]	**4** (recovery, %)
1	2-pyrimidyl (**4a**)	57	62	34
2	phenyl (**4b**)	2	4	95
3[b]	phenyl (**4b**)	4	4	95
4	2-pyridyl (**4c**)	28	31	59
5	2-(4-*tert*-butyl)pyrimidyl (**4d**)	27	50	53

[a] Isolated yields besed on the amount of **4** used. [b] 1.0 equiv of pyrimidine was added.

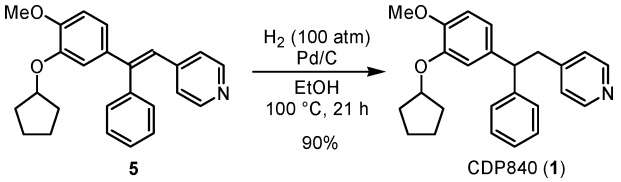
critical in this cross-coupling reaction. Although the use of CH_3CN, EtOH, and *t*-BuOH had a detrimental effect in the coupling efficiency (entries 2−4), the use of amide-based solvents such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), and 1,3-dimethyl-2-imidazolidinone (DMI) furnished **5** in higher yields (entries 5−7). In particular, the use of DMI afforded the desired **5** in 66% yield when 3.0 equiv of 4-pyridylboronic acid was employed (entry 8). Further screening of Pd catalysts (e.g. $PdCl_2(PPh_3)_2$, $Pd(OAc)_2/P(OPh)_3$, $Pd[P(t\text{-}Bu)_3]_2$) was also investigated, but they all turned out to be less active than $Pd(PPh_3)_4$ in this cross-coupling.

Initially, we introduced the catalyst-directing 2-pyrimidyl group on sulfur in the vinyl sulfide strucure to accomplish a "hard-to-achieve" Pd-catalyzed double C−H arylation (**2** → **4**).[3] During the present investigation, we found an additional bonus by attaching the 2-pyrimidyl group on sulfur in the cross-coupling at the alkenyl−sulfur bond with arylboronic acids. Listed in Table 2 are the results of the Liebeskind−Srogl-type cross-coupling reaction of various vinyl sulfides **4** with 4-pyridylboronic acid.

As already mentioned, the reaction of **4a** with 4-pyridylboronic acid afforded **5** in 57% yield under the influence of $Pd(PPh_3)_4$ and CuTC (Table 2, entry 1). 4-Pyridyl-2-pyrimidine (**6a**), another possible cross-coupling product, was also obtained in 62% yield. These results clearly indicate that both alkenyl and pyrimidyl groups on sulfur are transferred into the coupling product. The reaction with the phenyl analogue **4b** was totally sluggish under otherwise identical conditions, giving **5** and **6b** in very low yield (entry 2). The addition of pyrimidine (1.0 equiv) into the reaction system did not promote the reaction either (entry 3). Thus, it is obvious that the pyrimidyl group should be attached to sulfur to achieve the cross-coupling at the alkenyl−sulfur bond. The 2-pyridyl analogue **4c** was found to be a somewhat better substrate than the phenyl analogue **4b** (entry 4). Interestingly, the introduction of a *tert*-butyl group at the 4-position of the pyrimidine ring (**4d**) had a pronounced detrimental effect on the coupling efficiency (entry 5).

There may be two possible explanations for the beneficial effect of a 2-pyrimidyl group in the cross-coupling

SCHEME 4. Hydrogenation of 5



at the alkenyl−sulfur bond. As we previously found in the iron-catalyzed cross-coupling of alkenyl 2-pyrimidyl sulfides with Grignard reagents,[13] the 2-pyrimidyl group might be acting as a directing group to a certain metal species (Pd or Cu) to help the reacting C=C bond to participate effectively in the desired cross-coupling manifold through a complex-induced proximity effect. The substantial decrease in coupling efficiency caused by the introduction of a bulky *tert*-butyl group on the pyrimidine ring (**4d**), which should interrupt such an attractive pyrimidyl−metal interaction, is in line with such a directed cross-coupling scenario.

Alternatively, the cross-coupling at the 2-pyrimidyl−sulfur bond might be faster than that at the desired alkenyl−sulfur bond. Such a cross-coupling should generate a structurally less congested alkenyl thiolate (or thiol), which can then participate in the cross-coupling. In such circumstances, 2-pyrimidyl sulfide can be regarded as a "masked" thiol. The fact that the yields of **6** (aryl group transfer) are comparable or greater than those of **5** (alkenyl group transfer) implicates such a reactivity order (heteroaryl > aryl ≈ β,β-diarylvinyl).[16]

With the desired triarylethene **5** in hand, the reduction of the C=C bond of **5** remained to be conducted for the synthesis of CDP840 (Scheme 4). As was somewhat expected from the nonplanar structure of triarylethenes,[3] the reduction of the C=C core of **5** required harsh conditions. All attempts to accomplish this task through metal−complex-catalyzed (homogeneous) hydrogenation or hydrometalation/protodemetalation sequence resulted in failure. Finally we found that heating a suspension of **5** and Pd/C in EtOH at 100 °C under 100 atm of H_2 afforded CDP840 (**1**) in 90% isolated yield (Scheme 4).

In summary, we have achieved a short synthesis of CDP840 using 2-pyrimidyl vinyl sulfide as a platform (3 steps from **2**, 52% overall yield). During these investigations, we found an additional bonus by attaching the 2-pyrimidyl group on the sulfur of the alkenyl sulfide structure in the Liebeskind−Srogl-type cross-coupling reaction. Although a racemic reduction was applied in this work, the employment of an asymmetric catalyst in the final step (hydrogenation) would straightforwardly produce optically active CDP840. The asymmetric synthesis will be reported elsewhere.

Experimental Section

***E*-2-(3-Cyclopentyloxy-4-methoxy)phenyl-2-phenylethenyl 2-Pyrimidyl Sulfide (4a).** To a solution of $Pd[P(t\text{-}Bu)_3]_2$ (38.3 mg, 0.075 mmol) in toluene (6 mL) were added iodobenzene (306 mg, 1.50 mmol), Et_3N (455 mg, 4.50 mmol), and **2** (207 mg, 1.50 mmol). The reaction mixture was stirred for 4 h at 60 °C.

(16) Liebeskind has already found that the transfer ability (from sulfur) of a certain heteroaryl group (2-nitro-2-pyridyl group) is much higher than that of the *p*-tolyl group in the Pd-catalyzed cross-coupling using sulfides.[14b]

After the consumption of sulfide, **3** (525 mg, 1.65 mmol) was added to the reaction mixture and the resultant mixture was stirred for an additional 18 h at 90 °C. After the reaction mixture was cooled to room temperature, it was filtered through a short silica gel pad (eluent: EtOAc) and the filtrate was concentrated in vacuo. The recrystallization of residual solids from hexane/EtOAc (5/1) afforded **4a** (525 mg, 87%, *E*:*Z* = 97:3) as colorless crystals. IR (KBr) 2961, 1260, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 3.0 Hz, 2H), 7.62 (s, 1H), 7.42−7.32 (m, 5H), 6.98 (t, J = 3.0 Hz, 1H), 6.88 (dd, J = 5.3, 1.3 Hz, 1H), 6.84 (d, J = 1.3 Hz), 6.79 (d, J = 5.3 Hz, 1H), 4.69 (m, 1H), 3.84 (s, 3H), 1.87−1,78 (m, 6H), 1.58−1.54 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 170.5, 157.2, 149.6, 140.9, 136.3, 134.3, 129.5, 128.2, 127.7, 120.0, 117.0, 116.9, 114.6, 111.5, 80.5, 58.1, 32.9, 24.2. LRMS (EI) *m/z* 404 (M^+). HRMS (EI) calcd for $C_{24}H_{24}N_2O_2S$ 404.1558, found 404.1556.

***E*-2-(3-Cyclopentyloxy-4-methoxy)phenyl-2-phenyl-1-(4-pyridyl)ethene (5).** The mixture of $Pd(PPh_3)_4$ (11.6 mg, 0.010 mmol), **4a** (80.9 mg, 0.200 mmol), 4-pyridylboronic acid (73.7 mg, 0.600 mmol), and copper thiophene-2-carboxylate (114.4 mg, 0.600 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI) (1.5 mL) was stirred for 18 h at 60 °C under argon. The resultant mixture was cooled to room temperature and filtered through a short silica gel pad (eluent: EtOAc). The filtrate was washed with 28% aq NH_3, water, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by silica gel flash column chromatography (eluent; hexane/EtOAc = 5/2 to 5/3) afforded **5** (49.0 mg, 66%) as a yellow gum and recovered **4a** (18.6 mg, 23%). IR (neat) 3015, 2963, 1266, 812 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 2H), 7.36−7.32 (m, 3H), 7.18−7.15 (m, 2H), 6.85−6.78 (m, 6H), 4.70−4.66 (m, 1H), 3.85 (s, 3H), 1.85−1.80 (m, 6H), 1.58−1.52 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 150.4, 149.2 (2×), 147.2, 146.9, 145.0, 139.3, 134.9, 129.9 (2×), 128.6 (2×), 128.0, 123.6, 123.3 (2×), 120.6, 114.6, 114.4, 80.5, 56.1, 32.9 (2×), 24.2 (2×). LRMS (EI) *m/z* 371 (M^+). HRMS (EI) calcd for $C_{25}H_{25}NO_2$ 371.1883, found 371.1884.

2-(3-Cyclopentyloxy-4-methoxy)phenyl-2-phenyl-1-(4-pyridyl)ethane (CDP840, 1). The mixture of **5** (45.1 mg, 0.121 mmol), Pd/C (25 mg, 5%), and EtOH (3 mL) was stirred at 100 °C for 21 h under H_2 (100 atm) in an autoclave. After being cooled to room temperature, the mixture was filtered and concentrated. Purification of the residue by silica gel flash column chromatography (eluent: hexane/EtOAc = 5/3) afforded CDP840 (**1**) (40.8 mg, 90%) as a colorless oil. IR (neat) 2959, 1262, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 3.0 Hz, 2H), 7.27−7.23 (m, 2H), 7.18−7.15 (m, 3H), 6.92 (d, J = 3.8 Hz, 2H), 6.73 (d, J = 5.3 Hz, 1H), 6.68 (dd, J = 5.3, 1.3 Hz, 1H), 6.64 (d, J = 1.0 Hz, 1H), 4.65−4.62 (m, 1H), 4.14 (t, J = 5.0 Hz, 1H), 3.78 (s, 3H), 1.82 (m, 6H), 1.57−1.55 (m, 2H). ^{13}C NMR (100 Hz, $CDCl_3$) δ 149.4, 149.1 (2×), 148.5, 147.2, 143.8, 135.8, 128.3 (2×), 127.6 (2×), 126.3, 124.4 (2×), 119.9, 115.3, 111.9, 80.5, 56.1, 51.6, 41.7, 32.9, 32.8, 24.2 (2×). LRMS (EI) *m/z* 373 (M^+). HRMS (EI) calcd for $C_{25}H_{27}NO_2$ 373.2043, found 373.2046.

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Supporting Information Available: Additional experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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