Aromatization of Enamines Promoted by a Stoichiometric Amount of Palladium(II) Salts: A Novel Method for the Synthesis of Aromatic Amines

Teruhiko Ishikawa,* Eiji Uedo, Rie Tani, and Seiki Saito*

Department of Bioscience and Biotechnology, Faculty of Engineering, Okayama University, Tsushima, Okayama, Japan 700-8530

seisaito@biotech.okayama-u.ac.jp

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Enamines (**1a**−**r**) prepared from cyclohexanones, cyclohexane-1,3-diones, or tetralones led to arylamines (**2a**−**r**) in one pot when treated with a stoichiometric amount of palladium salts [$PdCl_2$-$(MeCN)_2$] in acetonitrile in the presence of triethylamine at room temperature or at elevated temperature, in some cases for 5 min to 2 h. The initial electrophilic attack of palladium chloride on the β-carbon of the enamines led to a σ-palladium species (**8**) which triggered a series of reactions (→ **9** → **10** → **11** → **12**) destined for aromatization to give **2a**−**r** in good yields. The intervention of such a σ-palladium species has been attested by a trapping experiment. On the basis of this reaction mechanism, we have developed another new process capable of transforming acyclic compounds having 6-en-2-one frameworks (**16**, **23**, **25**) to arylamines (**2s**−**u**) when their enamines were treated under the similar conditions as above, featuring again the formation of σ-palladium species such as **8** as the initial key intermediate.

Introduction

Heteroatom-substituted carbon−carbon double bonds such as enamines or enol silyl ethers have played a unique role in organic synthesis when reacted with transition metal salts, and two cases have been reported so far.[1,2] First, when reacted with mercuric acetate, enamines led to an iminium ion intermediate bearing a covalent carbon−mercury bond which was highly amenable to hydride reduction and hence served as a precursor for tertiary amines (eq 1).[1] Second, enol silyl ethers led to α,β-unsaturated carbonyl compounds via palladium enolate when reacted with palladium acetate (eq 2).[2] As the third representative reaction along similar lines, we found for the first time that the reaction of palladium(II) salts with cyclohexanone-based enamines provided a novel method for the synthesis of aromatic amines (eq 3).[3] In this reaction the initial formation of a σ-palladium species triggered a series of reactions destined for aromatization under very mild conditions (room temperature, <2h) to give aniline or naphthylamine derivatives of significant diverse applications.[4] We have also been intrigued with the combination of the present elementary process involving the formation of the σ-palladium species with well-known palladium chemistry. Such an idea, when applied to acyclic 6-en-2-one frameworks, was expected to make sense in realizing the acyclic enone to aromatic amine conversion in one pot (eq 4). Highly promising results in this context will also be reported.

Results and Discussion

Aromatization of Cyclohexanone-Based Enamines. When treated with $PdCl_2$·$(MeCN)_2$ (200 mol %) and Et_3N (500 mol %) in acetonitrile at room temperature for 2 h (standard conditions), for instance, commercially available enamine (**1a**) gave *N*-phenylmorpholine (**2a**) in 86% yield after chromatographical purification by silica gel column without any appreciable side product.[5] The results of enamine aromatization under such conditions are listed in Table 1.

The use of a variety of both cycloalkanones (cyclohexanone derivatives and α- or β-tetralones) and amines (morpholine, piperidine, pyrrolidine, *N*-methylaniline, and amino acid esters such as proline methyl ester) allowed us to obtain a variety of aniline and naphthylamine derivatives (**2a**−**l**). It is worthy of note that, to the best of our knowledge, the present aromatization is the only method by which we can introduce a phenyl group on a nitrogen atom of an amino acid (**2i**, entry 9). A vitamin L_1 (anthranilic acid) derivative (**2k**) was

(1) Bach, R. D.; Mitra, D. K. *J. Chem. Soc., Chem. Commun.* **1971**, 1433−1434.

(2) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013. (b) Baba, T.; Nakano, K.; Nishiyama, S.; Tsuruya, S.; Masai, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1697−1699. See also: Theissen, R. J. *J. Org. Chem.* **1971**, *36*, 752−757.

(3) Only one fragmentary description is available that an enamine prepared from cyclohexanone and 2-(methoxymethyl)pyrrolidine can be oxidized to lead to an aromatic amine on treatment with $Pd(OAc)_2$ in the presence of iodobenzene, Et_3N, and Ph_3P in DMF at 80 °C, while the Heck coupling of iodobenzene proceeded to give a biphenyl. See: de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88−110.

(4) Transition metal-catalyzed amination of aromatic halides or sulfonates is one of the most prevalent ways to prepare this class of compounds; for pioneering work in this area, see: (a) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927−928. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970. See also: (c) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (d) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067. (e) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818 and references therein. For recent interesting work using molecular nitrogen in this area, see: Hori, K.; Mori, M. *J. Am. Chem. Soc.* **1998**, *120*, 7651−7652.

(5) We can quickly recognize how mild the reaction conditions were by remembering those for the aromatization of 4,5,6,7-tetrahydroindazole to indazole (heating a solution of Decaline under reflux (>190 °C) for 24 h in the presence of Pd−charcoal). See: Ainsworth, C. *Organic Syntheses*; Wiley: New York, 1963; Vol. IV, pp 536−539.

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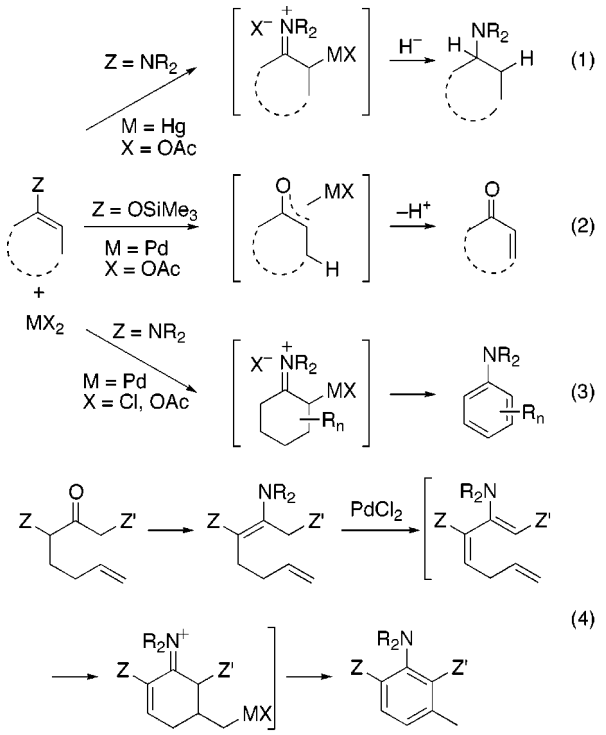
Scheme 1



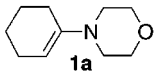
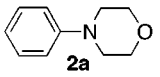
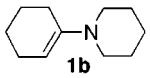
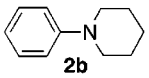
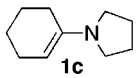
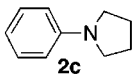
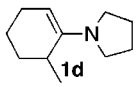
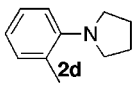
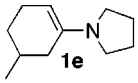
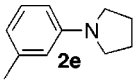
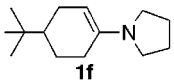
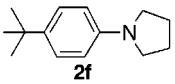
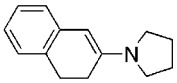
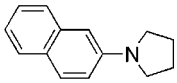
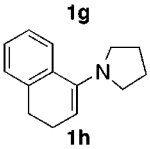
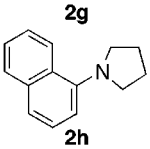
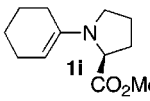
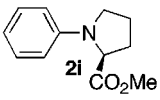
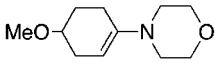
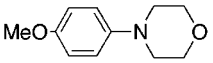
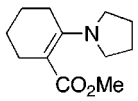
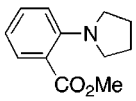
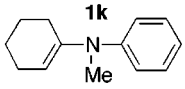
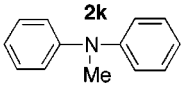
obtained from a ketoester-based enamine (**1k**) (entry 11) though it required elevated temperature.

In addition, the present method can be applied to the synthesis of *m*-aminophenols from 1,3-cyclohexanediones (Scheme 2). For instance, on treatment of the aminoenone (**1m**), prepared from 2-methylcyclohexane-1,3-dione in quantitative yield, with TBSOTf in THF in the presence of Et_3N (5 equiv) at 0 °C for 1 h followed by the addition of $PdCl_2(CH_3CN)_2$ (1 eq) and heating the mixture at 50 °C for 1 h led to *N*-[*o*-methyl-*m*-(*tert*-butyldimethylsilyloxy)phenyl]pyrrolidine (**2m**) in 42% overall yield through a three-step process as indicated in Scheme 2: **2n** was also obtained likewise in 33% overall yield from 1,3-cyclohexanedione.

We attempted to introduce other amino-substituents along this scheme using aliphatic secondary amines such as dimethylamine, diethylamine, dibenzylamine, or benzylmethylamine. To the marked contrast to the case of pyrrolidine, the direct formation of the desired aminoenones from 1,3-cyclohexanediones resulted in complex mixture. However, an indirect method via the acetoxy enone (**4**) as shown in Scheme 3 gave the temporary answer to this problem. Thus, the reactions of **4** with the secondary aliphatic amines (1.2 equiv) in THF were carried out under the conditions indicated in Scheme 3 followed by the addition of excess TBSOTf and Et_3N at −78 °C and stirring the resulting mixture at −78 °C to 0 °C for 1 h. Further stirring of the mixture at 0 °C for 0.5 h and at 70 °C for 5 min in the presence of $PdCl_2(CH_3CN)_2$ furnished the desired aminophenol derivatives (**2o**−**r**) probably via the intermediate **5** albeit in low yield but pure state after chromatographical purification although accompanied by the side product (**6**: 10%).

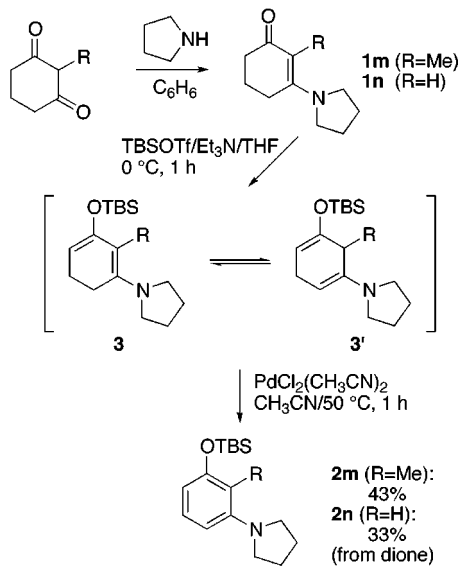
Mechanism of the Aromatization of Cyclohexanone-Based Enamines. The plausible mechanism of this aromatization is outlined in Scheme 4. Electrophilic attack of a palladium salt on the β-carbon of enamines (**1**) produces a palladium substituted iminium ion intermediate (**8**), in which β-hydride elimination smoothly takes place to give an α,β-unsaturated iminium ion (**9**). The reversible reaction between palladium salts and **1** might result in complexation at nitrogen to give **7**, but this species has no chance to undergo further reactions except for the reverse reaction under standard conditions. In order for **9** to be converted into an aniline framework, the iminium ion **9** must generate the second enamine intermediate (**10**) through deprotonation followed by the same sequence of reactions as **1** → **8** → **9**, leading to **12** successively via **10** and **11**. The final deprotonation from **12** terminates this aromatization process to give **2**.[6] In support of this mechanism, 200 mol % of palladium salt was required (**1** → **3** and **6** → **7** conversions) for the

Table 1. Summary of the Aromatization of Enamines[a]

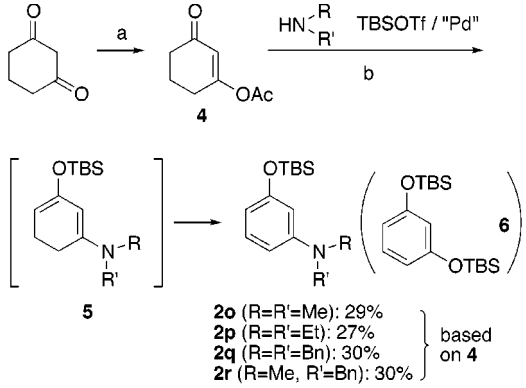
Entry	Enamine	Product	Yield/%[b]
1	 **1a**	 **2a**	86 (90)
2	 **1b**	 **2b**	74
3	 **1c**	 **2c**	89
4[c]	 **1d**	 **2d**	70
5[d]	 **1e**	 **2e**	94
6	 **1f**	 **2f**	79
7[e]	 **1g**	 **2g**	99 (99)
8[e]	 **1h**	 **2h**	95
9	 **1i**	 **2i**	71
10	 **1j**	 **2j**	55
11[f]	 **1k**	 **2k**	57
12[g]	 **1l**	 **2l**	47

[a] 200 mol % $PdCl_2(MeCN)_2$/500 mol % Et_3N/CH_3CN/rt for 2 h. [b] For chromatographically pure products; yields in parentheses for $Pd(OAc)_2$/THF. [c] A mixture of enamine regioisomers (7:3). [d] A mixture of enamine regioisomers (1:1). [e] 100 mol % of $PdCl_2(MeCN)_2$/300 mol % Et_3N. [f] 1% of **2c** as byproduct. [g] At elevated temperature (80 °C) for 0.5 h. [h] Enamine, not purified.

Scheme 2



Scheme 3



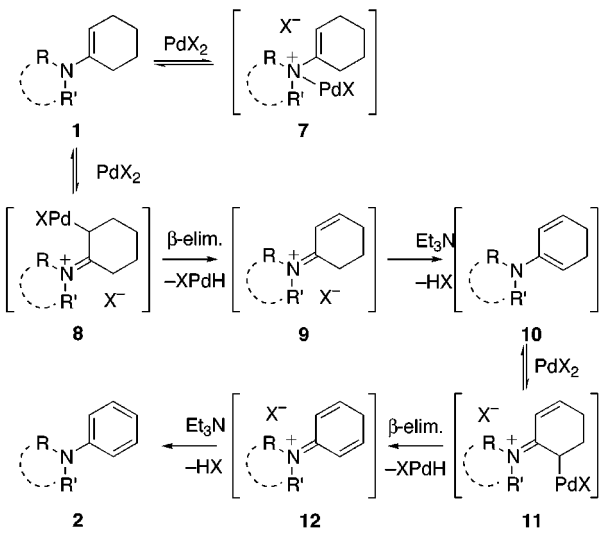
(a) 1.5 × AcCl/2 × C_6H_5N/CH_2Cl_2/0 °C, 10 min; (b) 1. 2 × amine/THF/0 °C, 2 h (R=R'=Me), 0°C—rt, 1 h (R=R'=Et), 50°C, 0.5 h (R=R'=Bn), rt, 0.5 h (R=Me, R'=Bn) , 2. 2 × TBSOTf/5 × Et_3N/–78 °C—rt, 3. 1 × $PdCl_2(CH_3CN)_2$/0 °C, 0.5 h and 70 °C, 5 min

reaction to be completed except for entries 7 and 8 in which 100 mol % was enough.

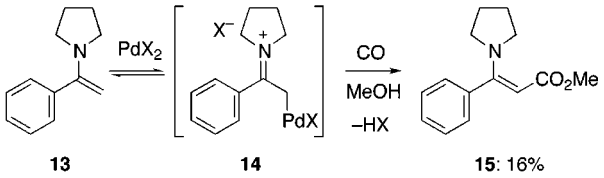
To attest to the intervention of the σ-palladium intermediates, we took up an acetophenone-based enamine (**13**). This enamine can also lead to the corresponding intermediate (**14**), which would be trapped through an oxidative carbonylation reaction[7] because there is no opportunity for **14** to undergo β-hydride elimination. In fact, the reaction of **13** with the palladium salt followed by CO treatment in methanol gave **15** (Scheme 5). Although the yield of **15** was low,[8] its formation revealed by itself the intervention of the σ-palladium intermediate **14**.

Strategy for the Conversion of Acyclic Enone to Aromatic Amines. A novel idea by which, if realized, we can transform acyclic enones to arylamines in one pot is based on the recognition of the σ-palladium species

Scheme 4



Scheme 5



intervention. Thus, when an acyclic ketoester-based enamine (**17**) without isolation and purification was treated with $PdCl_2$·$(MeCN)_2$ (200 mol %) and Et_3N (500 mol %) in acetonitrile at 80 °C for 1 h, a methyl-substituted anthranilic acid derivative (**2s**) was obtained in 37% overall yield from **16**. As shown in Scheme 6, a combination of elementary reactions appeared in Scheme 4, corresponding to **17** → **18** → **19** → **20** in this case, with the well-known organopalladium reaction (**20** → **21**) playing an important role in this transformation.

Another acyclic ketoester **23** was also a successful substrate for the similar transformation as **16** → **2s**. In this case the rather stable enamine **24** was purified by bulb-to-bulb distillation and was treated with palladium(II) species to give the desired **2t** in 45% yield from **24**. Furthermore, this basic strategy turned out to be applicable to a more simple 6-en-2-one framework such as **25**,[9] which was available through titanium tetrachloride-mediated Michael addition of allyl silane to 1-acetylcyclopentene which was provided through Rupe rearrangement of a 1,2-adduct of cyclopentanone and ethynylmagnesium bromide. An Indan derivative (**2u**) was the product of transformation of this class and was obtained more efficiently (57% yield from **25**) probably via **26**.

Although exhaustive examinations for the above-mentioned conversion have not been conducted yet, these results suggest that this novel route to aromatic amines from acyclic precursors with the 6-en-2-one framework would be of high synthetic potential and open a general method for efficient access to tailored aromatic amines.

Attempted Construction of a Catalytic System. When **1c** was treated with 10 mol % $PdCl_2(MeCN)_2$ complex in the presence of an oxidant such as $CuCl_2$ (300 mol %) and Et_3N (400 mol %) in acetonitrile at room

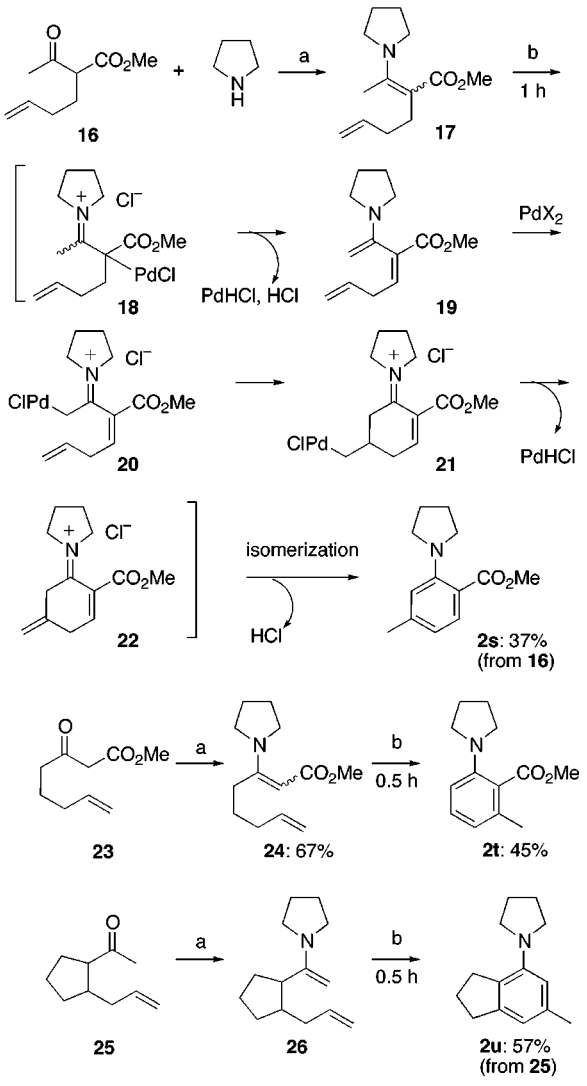
(6) Enamine prepared from 3,3,5,5-tetramethylcyclohexanone was recovered unchanged under standard conditions, which also supports the proposed mechanism (**3** → **5** conversion to be prohibited).

(7) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146−151.

(8) Because of the reducing ability of CO, the palladium(II) salt was quickly reduced to metallic state under the reaction conditions. This is probably the reason **15** was isolated only in very low yield (16%).

(9) House, H. O.; Gaa, P. C.; VanDerveer, D. *J. Org. Chem.* **1983**, *48*, 1661−1670.

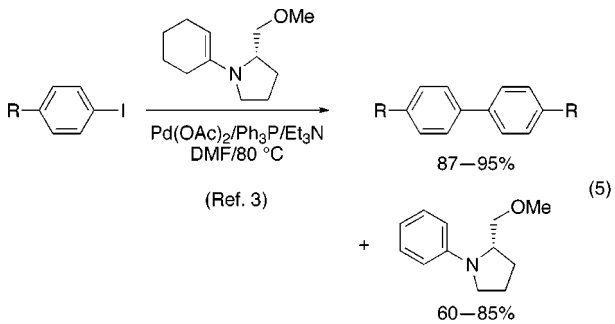
Scheme 6



(a) Pyrr./PhH; (b) $2 \times PdCl_2(CH_3CN)_2/5 \times Et_3N/80$ °C

temperature for 30 min, **2c** was obtained in 20% yield. This result means that the Pd(II) species effected dehydrogenation catalytically with a turnover number of 4. Except for this hopeful result, however, we have examined in vain other oxidants such as benzoquinone or alkyl nitrites.

Recently, Meijere and Bräse have reported that an enamine can be employed as a reducing agent in palladium-catalyzed homo coupling of haloarenes leading to biaryls (eq 5).[3]



(5)

This reaction suggests that the haloarenes might serve as oxidant in the present case. It turned out, however, that several enamines **1a**−**c** in place of 1-[1-(2-methoxymethyl)pyrrolidinyl]cyclohexene did not act as the reductant for this process (eq 5). This result clearly indicated that the haloarenes such as *p*-methoxyiodobenzene did not serve as oxidant in our case and only the specific enamine used by Meijere and Bräse can function as reductant in eq 5.

Concluding Remark. From a chronological point of view, electrophilic aromatic substitution (S_E1 mechanism involving nitration followed by reduction[10] or direct amination[11]) is the first generation of aromatic amine synthesis followed by nucleophilic aromatic substitution (S_NAr,[12] benzyne,[13] or $S_{RN}1$[14] mechanism) and transition metal-catalyzed amination of aromatic halides[4] as the second and third generation, respectively. The third generation method has now become the most prevalent one, the original reaction of which was reported in 1983 by Kosugi,[4a] and the elementary processes involved therein were rationalized in 1994 by Hartwig,[4b] triggering off modern activity in this area. The present reaction may be a first step toward a potentially useful reaction to make aromatic amines featuring aliphatic-to-aromatic transformation.[15] We could make use of this novel transformation in synthetic objectives which are difficult to achieve relying on the previous methods. In any event, the most important task remaining is to reduce the stoichiometric use of palladium salts to a catalytic amount, and this is now under active investigation with regard to oxidants, ligands, and solvents.

Experimental Section

General. Melting points are not corrected. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz using $CDCl_3$ as a solvent. The chemical shifts (δ) are given in parts per million relative to internal $CHCl_3$ (7.26 ppm for ^1H) or $CDCl_3$ (77 ppm for ^{13}C). ^1H-H COSY experiments were obtained at 300 MHz. FR−IR spectra were recorded using NaCl cells or mixtures of compound/KBr. Analytical thin-layer chromatography was performed on Merck, precoated silica gel 60 F-254 (0.25 mm thickness). Column chromatography was performed on a Merck silica gel 60 7734 using an appropriate ratio of ethyl acetate−hexane mixed solvent and is abbreviated as CC. Elemental analyses were carried out by Dr. Miyoko Izawa of this laboratory. All reactions, unless otherwise noted, were conducted under a nitrogen or an argon atmosphere. Liquid reagents are transferred via a dry hypodermic syringe and added through a rubber septa wired onto a reaction flask from which a steady stream of inert gas was flowing. Acetonitrile (CH_3CN), triethylamine (Et_3N), dichloromethane (CH_2Cl_2), and benzene were freshly distilled from CaH_2 prior to use. Methanol was distilled from magnesium turnings under argon. Tetrahydrofuran (THF) was distilled from benzophe-

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(15) Formation of aromatic rings through enamine annulation reported recently gains entry to this category: Wang, C.; Kohn, H. *Org. Lett.* **2000**, *2*, 1773−1775.

none-ketyl prior to use. $Pd(OAc)_2$ and $PdCl_2$ were commercial reagents.

Palladium chloride−acetonitrile complex $[PdCl_2(CH_3CN)_2]$ was prepared by heating a suspension of $PdCl_2$ in acetonitrile under reflux and by cooling the thus-obtained solution to room temperature: the desired crystalline complex precipitated and was collected by filtration. Enamines were prepared after the reported procedure (Hünig, S.; Lücke, E.; Brenninger, W. *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. V, pp 808−809).

General Procedure for Aromatization of Enamines. Method A. To a stirred suspension of $PdCl_2(CH_3CN)_2$ (309 mg, 1.19 mmol) in acetonitrile (3 mL) were added Et_3N (0.41 mL, 3.0 mmol) and then enamine (0.59 mmol) dissolved in acetonitrile or dichloromethane (1 mL) at room temperature. The mixture was stirred at room temperature for 2 h. After filtration through a short Florisil pad, the filtrate was concentrated by a rotary evaporator. The residue was purified by CC.

Method B. $Pd(OAc)_2$ (267 mg, 1.19 mmol) and THF were employed in place of $PdCl_2(CH_3CN)_2$ and acetonitrile, respectively.

Method C. The same mixture as that of method A was heated at 80 °C under stirring for 0.5 h.

4-Phenylmorpholine (2a). Method A: colorless crystals (84 mg, 86%) (method B, 90%); mp 48−50 °C (lit.[16] mp 51−54 °C); ^{1}H NMR δ 3.15−3.20 (m, 4H), 3.85−3.90 (m, 4H), 6.84−6.96 (m, 3H), 7.24−7.34 (m, 2H); ^{13}C NMR δ 49.4, 66.9, 115.7, 120.0, 129.1, 151.3; IR (KBr) 2855, 1598, 1376, 1120, 772 cm^{-1}.

1-Phenylpiperidine (2b).[1] Method A: colorless oil (35 mg, 74%); ^{1}H NMR δ 1.61−1.71 (m, 2H), 1.75−1.86 (m, 4H), 3.21−3.28 (m, 4H), 6.75−6.89 (m, 1H), 7.01−7.06 (m, 2H), 7.30−7.38 (m, 2H); ^{13}C NMR δ 24.3, 25.8, 50.6, 116.5, 119.1, 128.9, 152.2; IR (film) 2933, 1597, 1383,1237, 756 cm^{-1}.

1-Phenylpyrrolidine (2c). Method A: colorless oil (81 mg, 89%); ^{1}H NMR δ 2.01−2.11 (m, 4H), 3.30−3.39 (m, 4H), 6.60−6.76 (m, 3H), 7.25−7.33 (m, 2H); ^{13}C NMR δ 25.4, 47.5, 111.6, 115.3, 129.1, 147.9; IR (film) 2962, 1595, 1370, 1260, 1025, 798 cm^{-1}.

***N*-(2-Methylphenyl)pyrrolidine (2d).** Method A: colorless oil (33 mg, 70%); ^{1}H NMR δ 1.94−2.06 (m, 4H), 2.37 (s, 3H), 3.18−3.30 (m, 4H), 6.83−6.96 (m, 2H), 7.15−7.21(m, 2H); ^{13}C NMR δ 20.5, 24.9, 51.0, 115.7, 120.2, 126.2, 126.6, 128.6, 131.6, 149.3; IR (KBr) 2965, 1493, 753, 716 cm^{-1}. Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.71; H, 9.22.

***N*-(3-Methylphenyl)pyrrolidine (2e).** Method A: colorless oil (44 mg, 94%); ^{1}H NMR δ 1.96−2.06 (m, 4H), 2.35 (s, 3H), 3.25−3.35 (m, 4H), 6.32−6.43 (m, 2H), 6.46−6.48 (m, 1H), 7.12−7.19 (m, 1H); ^{13}C NMR δ 21.8, 25.4, 47.6, 108.9, 112.3, 116.3, 129.0, 138.8, 148.0; IR (film) 2965, 1499, 803, 763 cm^{-1}.

***N*-(*p*-*tert*-Butylphenyl)pyrrolidine (2f).** Method A: colorless crystals (42 mg, 79%); mp 41.0−42.0 °C (lit.[17] mp 38−39 °C); ^{1}H NMR δ 1.29 (s, 9H), 1.90−2.03 (m, 4H), 3.25−3.31 (m, 4H), 6.54 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 25.5, 31.6, 33.8, 47.7, 111.3, 125.9, 137.9, 145.9; IR (KBr) 2961, 1524, 1364, 810 cm^{-1}.

***N*-(2-Naphthyl)morpholine (2g).** Method A: pale yellow crystals (101 mg, 99%); mp 91.0−91.5 °C; ^{1}H NMR δ 2.01−2.21 (m, 4H), 3.37−3.45 (m, 4H), 6.85 (m, 1H), 6.97−7.02 (m, 1H), 7.11−7.18 (m, 1H), 7.31−7.37 (m, 1H), 7.60−7.71 (m, 2H); ^{13}C NMR δ 25.5, 47.8, 104.6, 115.7, 121.1, 125.7, 126.1, 126.2, 127.6, 128.7, 135.2, 145.9; IR (KBr) 2962, 1513, 824, 739 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 85.11; H, 7.70.

***N*-(1-Naphthyl)pyrrolidine (2h).** Method A: colorless oil (95 mg, 95%); ^{1}H NMR δ 2.03−2.21 (m, 4H), 3.38−3.59 (m, 4H), 7.14 (d, J = 7.4 Hz, 1H), 7.45−7.66 (m, 4H), 7.89−7.98 (m, 1H), 8.32−8.39 (m, 1H); ^{13}C NMR δ 24.7, 52.6, 111.3, 121.1, 124.2, 124.7, 125.4, 125.8, 128.0, 128.2, 134.9, 147.6; IR (KBr) 2966, 1574,1399, 796, 769 cm^{-1}.

***N*-Phenyl-L-proline Methyl Ester (2i).** Method A: colorless crystals (99 mg, 71%); mp 72.0−74.0 °C; $[\alpha]^{32}_D$ = −13.9 (c 1.0, $CHCl_3$); ^{1}H NMR δ 2.05−2.43 (m, 4H), 3.36−3.48 (m, 1H), 3.60−3.69 (m, 1H), 3.78 (s, 3H), 4.30−4.36 (m, 1H), 6.58−6.65 (m, 2H), 6.75−6.82 (m, 1H), 7.25−7.34 (m, 2H); ^{13}C NMR δ 23.8, 30.9, 48.2, 52.1, 60.7, 111.8, 116. 6, 129.2, 146.5, 174.9; IR (KBr) 2950, 1750, 1598, 1506, 1370, 747 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.50; H, 7.51.

***N*-(4-Methoxyphenyl)morpholine (2j).** Method C: colorless crystals (40 mg, 36%); mp 71.0−73.3 °C (lit.[1] mp 71 °C, lit.[18] mp 73.3 °C); ^{1}H NMR δ 3.03−3.08 (m, 4H), 3.77 (s, 3H), 3.84−3.88 (m, 4H), 6.82−6.92 (m, 4H); ^{13}C NMR δ 50.8, 55.5, 67.0, 114.4, 117.8, 145.6, 153.9; IR (KBr) 2970, 2853, 1513, 1266, 818 cm^{-1}.

***N*-[(2-Methoxycarbonyl)phenyl]pyrrolidine (2k).** Method C: colorless oil (56 mg, 57%); ^{1}H NMR δ 1.90−1.99 (m, 4H), 3.20−3.29 (m, 4H), 3.88 (s, 3H), 6.67−6.81 (m, 2H), 7.27−7.34 (m, 1H), 7.55−7.59 (m, 1H); ^{13}C NMR δ 25.8, 50.8, 51.9, 113.9, 115.6, 117.0, 131.0, 131.7, 147.9, 169.5; IR (film) 2948, 1713, 1599, 1362, 1225, 747 cm^{-1}. Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.09; H, 7.20.

Diphenylethylamine (2l). Method A: pale yellow oil (35 mg, 48%); ^{1}H NMR δ 3.34 (s, 3H), 6.94−7.08 (m, 6H), 7.23−7.33 (m, 4H); ^{13}C NMR δ 40.2, 120.4, 121.2, 129.2, 149.0; IR (film) 2930, 1591, 1496, 749 cm^{-1}.

3-(1-Pyrrolidinyl)-2-methyl-2-cyclohexenone (1m). To a solution of 2-methylcyclohexane-1,3-dione (0.5 g, 3.96 mmol) in benzene (10 mL) was added pyrrolidine (2.0 mL), and the mixture was heated and liberated water was removed by percolating the azeotropic mixture down through a MS-3A pad over 0.5 h. The mixture was evaporated to give an oil, which was dried under high vacuum to give 1.05 g of **1m** as a pale brown gum (quant): ^{1}H NMR δ 1.89 (s, 3H), 1.75−1.90 (m, 6H), 2.26−2.33 (m, 2H), 2.21−2.28 (m, 2H), 2.46−2.53 (m, 2H), 3.46−3.54 (m, 4H); ^{13}C NMR δ 12.8, 20.5, 25.5, 30.3, 36.4, 51.2, 105.7, 162.8, 197.0; IR (film) 2949, 2871, 1611, 1544, 729 cm^{-1}.

***N*-(3-*tert*-Butyldimethylsiloxy-2-methylphenyl)pyrrolidine (2m).** To a solution of **1m** (87 mg, 0.49 mmol) in THF was added 0.34 mL (1.5 mmol) of Et_3N, and the mixture was cooled to −78 °C followed by the addition of 0.22 mL (0.60 mmol) of TBSOTf and continued stirring at −78 °C to room temperature for 2 h, followed by the addition of $PdCl_2(CH_3CN)_2$. The reaction was stirred at 50 °C for 1 h, filtered through a short Florisil pad, and mixed with saturated aqueous $NaHCO_3$ solution. This mixture was extracted with AcOEt, and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated by a rotary evaporator. The residue was purified by CC to give **2m** (36 mg, 43%) as a colorless oil: ^{1}H NMR δ 0.22 (s, 6H), 1.03 (s, 9H), 1.86−1.96 (m, 4H), 2.16 (s, 3H), 3.09−3.17 (m, 4H), 6.42−6.47 (m, 1H), 6.55−6.61 (m, 1H), 6.93−7.00 (m, 1H); ^{13}C NMR δ −4.19, 13.3, 18.3, 24.8, 25.7, 25.8, 51.3, 109.2, 111.7, 120.2, 125.6, 151.1, 154.7; IR (film) 2957, 2929, 2858, 1591, 1471, 837 cm^{-1}.

3-(1-Pyrrolidinyl)-2-cyclohexen-1-one (1n). To a solution of cyclohexane-1,3-dione (1.5 g, 13.4 mmol) in benzene (20 mL) was added pyrrolidine (3.0 mL), and the mixture was heated under reflux while liberated water was removed by percolating the azeotropic mixture down through a MS-3A pad for 0.5 h. The mixture was concentrated by a rotary evaporator, and the residue was further dried under a high vacuum to give **1n** (2.19 g, 99%) as a brown gum: ^{1}H NMR δ 1.92−2.04 (m, 6H), 2.26−2.33 (m, 2H), 2.42−2.49 (m, 2H), 3.15−3.26 (m, 2H), 3.38−3.49 (m, 2H), 5.06 (s, 1H); ^{13}C NMR δ 22.1, 24.7, 25.3, 27.9, 35.8, 47.9, 98.4, 163.5, 196.2; IR (KBr) 2945, 2870, 1553, 799 cm^{-1}.

***N*-[(3-*tert*-Butyldimethylsiloxy)phenyl]pyrrolidine (2n).** To a solution of **1n** (50 mg, 0.30 mmol) in THF was added Et_3N (0.20 mL, 1.5 mmol), and the mixture was cooled to −78 °C. To this cold mixture was added TBSOTf (0.07 mL, 0.30 mmol) and the solution was stirred at −78 °C to room temperature for 2 h followed by the addition of $PdCl_2$-

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(18) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133−1135.

$(CH_3CN)_2$. The resulting solution was stirred at 50 °C for 1 h, filtered through a short Florisil pad, mixed with saturated $NaHCO_3$ aqueous solution, and extracted several times with AcOEt. The combined organic solutions were dried (Na_2SO_4), filtered, and concentrated by a rotary evaporator to give an oily residue, which was purified by CC to give **2n** (26 mg, 33%) as a colorless oil: ^{1}H NMR δ 0.26 (s, 6H), 0.99 (s, 9H), 1.94−2.03 (m, 4H), 3.21−3.29 (m, 4H), 6.05−6.08 (m, 1H), 6.14−6.22 (m, 2H), 7.06 (t, 1H, J = 8.0 Hz); ^{13}C NMR δ −4.32, 18.2, 25.4, 25.7, 25.8, 47.6, 103.6, 105.1, 107.3, 129.6, 149.2, 156.6; IR (film) 2959, 2856, 1607, 1499, 829 cm^{-1}.

3-Acetoxy-2-cyclohexen-1-one (4). To a solution of cyclohexane-1,3-dione (2 g, 17.8 mmol) in CH_2Cl_2 (40 mL) was added pyridine (2.9 mL, 35.7 mmol), and the mixture was cooled to 0 °C. To this solution was added acetyl chloride (1.9 mL, 26.8 mmol) in a dropwise manner. The reaction was quenched by the addition of water and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated by a rotary evaporator to give an oil, which was purified by CC to give **4** (2.32 g, 85%) as a colorless oil: ^{1}H NMR δ 1.98−2.11 (m, 2H), 2.21 (s, 3H), 2.37−2.43 (m, 2H), 2.53 (dt, J = 1.3, 6.1 Hz), 5.78−5.82 (m, 1H); ^{13}C NMR δ 21.0, 21.0, 28.1, 36.5, 117.2, 167.1, 169.6, 199.5; IR (film) 1770, 1672, 922, 879 cm^{-1}.

1,3-*O*-Bis(*tert*-butyldimethylsilyl)resorcinol (6). ^{1}H NMR δ 0.20 (s, 12H), 0.99 (s, 18H), 6.36 (t, J = 2.3 Hz, 1H), 6.47 (m, 2H), 7.07 (t, J = 8.0 Hz, 1H); ^{13}C NMR δ −4.39, 18.2, 25.7, 112.3, 113.4, 129.5, 156.6; IR (film) 2956, 2931, 2860, 1587, 831 cm^{-1}.

[*O*-(*tert*-Butyldimethylsilyl)-3-*N*,*N*-dimethylamino]phenol (2o). To a solution of **4** (0.1 g, 0.65 mmol) in THF (1 mL) was added a solution of dimethylamine in THF (2 N, 0.65 mL, 1.3 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h, concentrated, and dried under high vacuum to give a pale yellow gum. The gum was dissolved in THF (1 mL), and the obtained THF solution was cooled to −78 °C. To this cold solution were slowly added Et_3N (0.45 mL, 3.25 mmol) and TBSOTf (0.3 mL, 1.3 mmol). The mixture was stirred at −78 to 0 °C for 1 h, and $PdCl_2(CH_3CN)_2$ (168 mg) was added to the mixture and the obtained mixture was stirred at 0 °C for 0.5 h and heated at 70 °C for 5 min. The mixture was filtered through a short Florisil pad, and the pad was rinsed with AcOEt. The combined organic solutions were concentrated by a rotary evaporator to give an oil, which was purified by CC to give **2o** (48 mg, 29%) as a colorless oil: ^{1}H NMR δ 0.22 (s, 6H), 1.00 (s, 9H), 2.93 (s, 6H), 6.21−6.27 (m, 2H), 6.37 (dd, J = 2.2, 8.2 Hz, 1H), 7.08 (m, 1H); ^{13}C NMR δ −4.3, 18.2, 25.8, 40.6, 104.7, 106.0, 108.4, 129.5, 152.0, 156.6; IR (film) 1606, 835 cm^{-1}.

[*O*-(*tert*-Butyldimethylsilyl)-3-*N*,*N*-diethylamino]phenol (2p). This compound was obtained by the same procedure as that for the synthesis of **2o** using diethylamine in place of dimethylamine, **2p** (27%) as a colorless oil: ^{1}H NMR δ 0.23 (s, 6H), 1.11 (s, 9H), 1.17 (t, J = 7.0 Hz, 6H), 3.33 (q, J = 7.0 Hz, 4H), 6.13−6.21 (m, 2H), 6.32 (m, 1H), 7.05 (m, 1H); ^{13}C NMR δ −4.3, 12.6, 18.2, 25.7, 44.4, 103.84, 105.3, 107.2, 129.6, 149.2, 156.8; IR (film) 2956, 2930, 2858, 1606 cm^{-1}.

[*O*-(*tert*-Butyldimethylsilyl)-3-*N*,*N*-dibenzylamino]phenol (2q). This compound was obtained by the same procedure as that for the synthesis of **2o** using dibenzylamine in place of dimethylamine, 30% yield, colorless oil: ^{1}H NMR δ 0.08 (s, 6H), 0.94 (s, 9H), 4.67 (s, 4H), 6.22−6.29 (m, 2H), 6.40−6.45 (m, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.25−7.41 (m, 10H); ^{13}C NMR δ −4.6, 18.2, 25.7, 54.5, 104.8, 105.9, 108.7, 126.8, 128.6, 129.8, 138.6, 150.4, 156.6; IR (film) 2956, 2930, 2858, 1606, cm^{-1}.

[*O*-(*tert*-Butyldimethylsilyl)-3-(*N*-benzyl-*N*-methyl)amino]phenol (2r). This compound was obtained by the same procedure as that for the synthesis of **2o** using benzylmethylamine in place of dimethylamine: 30% yield, colorless oil; ^{1}H NMR δ 0.15 (s, 6H), 0.97 (s, 9H), 3.01 (s, 3H), 4.52 (s, 2H), 6.22−6.27 (m, 2H), 6.39 (dd, J = 2.3, 8.2 Hz, 1H), 7.07 (m, 1H), 7.21−7.37 (m, 5H); ^{13}C NMR δ −4.4, 18.2, 25.7, 38.7, 56.6, 104.5, 105.8, 108.4, 126.7, 126.8, 128.5, 129.6, 139.0, 151.0, 156.6; IR (film) 2956, 2930, 2858, 1605 cm^{-1}.

Methyl 2-(1-Pyrrolidinyl)-4-methylbenzoate (2s). Method C (enamine **17** was not isolated): colorless oil (36 mg, 37% from **16**); ^{1}H NMR δ 1.89−1.98 (m, 4H), 2.32 (s, 3H), 3.19−3.28 (m, 4H), 3.86 (s, 3H), 6.51−6.56 (dd, J = 8.0, 0.8 Hz, 1H), 6.60 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 21.9, 25.8, 50.9, 51.8, 114.4, 114.5, 116.9, 131.2, 142.2, 148.2, 169.4; IR (film) 2948, 1716, 1606, 1500, 1229 cm^{-1}.

Methyl 2-Methyl-6-(1-pyrrolidinyl)benzoate (2t). To a solution of methyl 3-oxo-7-octenoate (**23**; 2.9 g, 17.0 mmol) in benzene (15 mL) was added pyrrolidine (2.1 mL, 25.5 mmol) and the mixture was heated under reflux while liberated water was removed by percolating the azeotropical mixture down through a MS-3A pad. The resulting dark solution was concentrated by a rotary evaporator to give a tar, which was purified by bulb-to-bulb distillation (Kugelrohr, 0.1 mm Hg, 130−140 °C) to give **24** (2.5 g, 67%) as a pale yellow oil. A part of this oil (0.1 g, 0.45 mmol) was dissolved in CH_3CN (3 mL), and to the mixture were added Et_3N (0.31 mL, 2.24 mmol) and $PdCl_2(CH_3CN)_2$ (232 mg, 0.9 mmol). The obtained suspension was heated at 90 °C and stirred at that temperature for 1 h. The mixture was filtered through a short Florisil pad and the filtrate was concentrated by a rotary evaporator followed by the addition of saturated aqueous $NaHCO_3$ solution. The mixture was extracted with AcOEt, and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated by a rotary evaporator to give an oil, which was purified by CC to give **2t** (44 mg, 45%) as a colorless oil: ^{1}H NMR δ 1.88−1.98 (m, 4H), 2.27 (s, 3H), 3.22−3.29 (m, 4H), 3.89 (s, 3H), 6.51−6.60 (m, 2H), 7.13 (dd, J = 8.5, 7.4 Hz, 1H); ^{13}C NMR δ 20.2, 25.8, 49.6, 50.8, 51.8, 111.5, 118.4, 129.8, 136.3, 146.2, 171.5; IR (film) 2966, 2871, 1720, 1589 cm^{-1}.

6-Methyl-4-(1-pyrrolidinyl)indan (2u). Method C (enamine **26** was not isolated), colorless oil (57 mg, 57% from **25**): ^{1}H NMR δ 1.89−1.96 (m, 4H), 1.95−2.06 (m, 2H), 2.29 (s, 3H), 2.82 (tt, J = 7.42, 7.41 Hz, 2H), 3.02 (t, 3H, J = 7.41 Hz, 2H), 3.32−3.38 (m, 4H), 6.31 (s, 1H), 6.55 (s, 1H); ^{13}C NMR δ 21.5, 25.3, 25.7, 33.1, 33.3, 49.9, 112.0, 115.2, 126.9, 136.7, 146.3, 146.4; IR (film) 2950, 2844, 1580, 1483, 1360, 821 cm^{-1}.

Methyl 2-(1-Pyrrolidinyl)cinnamate (15). To a suspension of $PdCl_2(CH_3CN)_2$ (150 mg, 0.58 mmol) in CH_3CN (5 mL) was added α-(1-pyrrolidinyl)styrene (0.1 g, 0.58 mmol), and the mixture was heated at 80 °C for 0.5 h, cooled to 0 °C, and allowed to stand under a carbon monoxide atmosphere (1 atm) for 1 h. To this mixture was added MeOH, and the resulting mixture was stirred at room temperature for 1 h followed by the addition of Et_3N. After filtration through a short Florisil pad, the filtrate was concentrated to give an oil, to which was added water. The mixture was extracted three times with AcOEt, and the combined organic solutions were dried (Na_2SO_4) and concentrated by a rotary evaporator to give an oil, which was purified by CC and finally recrystallization (ether−hexane) to give **15** (22 mg, 16%) as colorless crystals: mp 103 °C (dec); ^{1}H NMR δ 1.65−2.12 (br, 4H), 2.88−3.40 (br, 4H), 3.46 (s, 3H), 4.69 (s, 1H), 7.18−7.24 (m, 2H), 7.33−7.43 (m, 3H); ^{13}C NMR δ 25.2, 45.7 (br), 49.9, 84.3, 127.3, 128.0, 128.2, 137.6, 161.1, 168.2; IR (KBr) 2938, 1697, 1556, 962, 788 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41. Found: C, 72.47; H, 7.66.

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Supporting Information Available: Copies of NMR spectra (^{1}H and ^{13}C) for the arylamines (**2a**−**u**). This material is available free of charge via the Internet at http://pubs.acs.org.

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