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Electrophilic Aromatic Addition Reaction: Electrophilic Attack at an Aromatic H Substituent Position

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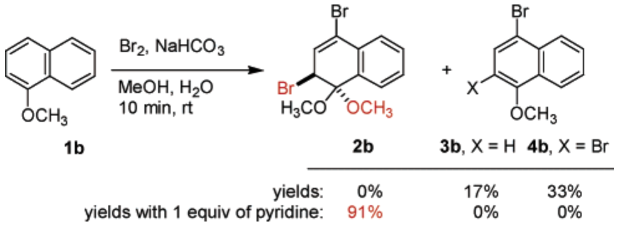
Received September 24, 2004



We report and propose a mechanism for an unusual electrophilic aromatic addition reaction (Ad$_E$Ar). During our preparation of 5,7-dibromo-8-methoxyquinaldine as a key intermediate in the synthesis of 7-bromoquinaldine-5,8-dione, direct bromination in either acidic or neutral conditions led only to the formation of 5-bromo-8-methoxyquinaldine. Under basic methanolic conditions, however, we unexpectedly obtained the 5,7-dibromo-8,8-dimethoxy-7,8-dihydroquinaldine adduct **2a**. This result not only allows for the functionalization of aromatic compounds via the addition adducts, but also introduces the possibility of an alternate mechanism for electrophilic substitution reactions.

Introduction

Although a wide variety of electrophilic species can attack aromatic rings and effect substitution, a single broad mechanism encompasses the large majority of electrophilic aromatic substitution reactions through the reversible formation of π and σ complexes.[1] In electrophilic substitution, the formation of the σ complex is generally the rate-determining step, with the aromatization occurring much faster than the addition of the nucleophile to the σ complex carbocation, but there are exceptions. Some authors indicate that nucleophile addition proceeds faster than deprotonation,[2] but the inability to isolate the intermediate adducts—due to their rapid rearomatization or further reaction to multiaddition products—forces investigators to draw conclusions regarding intermediate identity based solely on structural information obtained from the products. In cases where isolated adducts have been identified, the intermediates sometimes imply significant mechanistic differences when compared to the majority of known electrophilic aromatic substitutions. One example of this is the series of adducts identified in the nitration of furan, whose mode of decomposition differs greatly from that commonly seen in six-membered systems.[3] Moreover, when rearomatization by deprotonation is blocked, the known *ipso* attack of the nitro group at the substituted position also showed the possibility of electrophilic addition on benzenoid systems.[4]

Herein, we wish to report and propose a mechanism for an unusual electrophilic aromatic addition reaction (Ad$_E$Ar). During our preparation of 5,7-dibromo-8-methoxyquinaldine[5] as a key intermediate in the synthesis of 7-bromoquinaldine-5,8-dione,[6] direct bromination in either acidic or neutral conditions led only to the formation of 5-bromo-8-methoxyquinaldine. Under basic methanolic conditions, however, we unexpectedly obtained the 5,7-

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(1) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A*, 4th ed.; Kluwer Academic/Pluneum Publisher: New York, 2000; Chapter 10. (b) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240−248. (c) Ridd, J. H. *Acc. Chem. Res.* **1971**, *4*, 248−253. (d) Lenoir, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 854−857.

(2) (a) Hebel, D.; Rozen, S. *J. Org. Chem.* **1991**, *56*, 6298−6301. (b) Strand, J. W.; Kovacic, P. *J. Am. Chem. Soc.* **1973**, *95*, 2977−2982. (c) Kovacic, P.; Levisky, J. A. *J. Am. Chem. Soc.* **1966**, *88*, 1000−1005. (d) DeRosa, M.; Brillembourg, I. *J. Chem. Soc., Chem. Commun.* **1986**, 1585−1586. (e) DeRosa, M.; Nieto, G. C. *Tetrahedron Lett.* **1988**, *29*, 2405−2408.

(3) (a) Michels, J. G.; Hayes, K. J. *J. Am. Chem. Soc.* **1958**, *80*, 1114−1116. (b) Kolb, V. M.; Darling, S. D.; Koster, D. F.; Meyers, C. Y. *J. Org. Chem.* **1984**, *49*, 1636−1639.

(4) (a) Fischer, A.; Ramsay, J. N. *Can. J. Chem.* **1974**, *52*, 3960−3970. (b) Fisher, A.; Greig, C. C.; Roderer, R. *Can. J. Chem.* **1975**, *53*, 1570−1578. (c) Hahn, R. C.; Strack, D. L. *J. Am. Chem. Soc.* **1974**, *96*, 4335−4337

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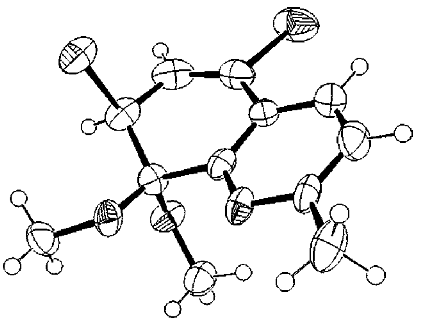
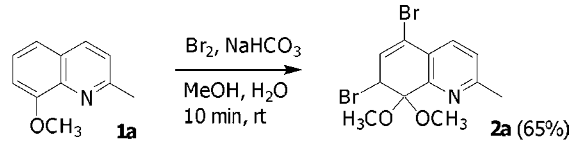


FIGURE 1. The X-ray structure of tetrahedral adduct **2a**.

SCHEME 1. The Addition Reaction of 8-Methoxyquinaldine (1a)



1a

2a (65%)

dibromo-8,8-dimethoxy-7,8-dihydroquinaldine adduct **2a** as the major product. To the best of our knowledge, this is the first reported isolation of an addition adduct at an aromatic H substituent position during the electrophilic aromatic substitution of a benzenoid compound. This result not only allows for the functionalization of aromatic compounds via the addition adducts, but also introduces the possibility of an alternate mechanism for electrophilic substitution reactions.

Results and Discussion

The conversion of 8-methoxyquinaldine **1a** by the treatment of bromine (3.0 equiv) in the presence of $NaHCO_3$ (3.5 equiv) occurred simply at room temperature (Scheme 1) and led to the formation of an intermediate, 5-bromo-8-methoxyquinaldine, which was indicated from TLC monitoring. After addition of water, the nearly pure addition product **2a** was precipitated as a racemic mixture. The proton NMR spectrum shows the H7 peak at 4.88 ppm (d, J = 7.0 Hz) as well as two different methoxy peaks, clearly proving the existence of the tetrahedral product.

Structural characterization of **2a** was further confirmed by elemental analysis, mass spectroscopy, and single-crystal X-ray analysis. X-ray crystallographic data for **2a** (Figure 1) illustrate that the bromine at C7 is in an axial-like orientation and is antiplanar with respect to one methoxy group, thereby placing H7 in an equatorial-like orientation, rendering it resistant to rearomatization by E2-elimination.

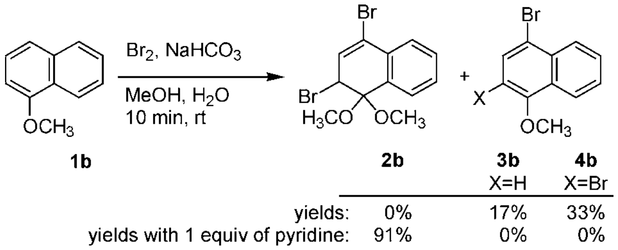
Upon first extension of this methodology to 1-methoxynaphthalene (**1b**), only the substitution products were obtained (Scheme 2). Interestingly, the TLC analysis used to monitor this reaction indicated the formation of nonisolable intermediates or addition adducts which differ from product. Because the pyridyl moiety structurally differentiates quinoline from naphthalene, we proposed that pyridine might play a role in sufficiently stabilizing addition adducts for isolation. To investigate the importance of the pyridine moiety, we added 1 equiv of pyridine into the reaction mixture under the same conditions. Surprisingly, we succeeded in obtaining the addition product in nearly quantitative yield (Scheme 2). This is the first isolation of the addition product at an aromatic H substituent position of a nonheterocyclic compound from the Ad_EAr reaction.

TABLE 1. Bromomethoxylation of 8-Methoxyquinaldine (1a) under Various Conditions[a]

entry	brominating agent	base (equiv)	yield of product (%)[b] **2a**	yield of product (%)[b] **3a**[c]
1	Br_2	$NaHCO_3$ (3.5)	65	
2	Br_2	$NaHCO_3$ (2)	51	25
3	Br_2	NaOMe (3)		90
4	Br_2	NaOMe (1)	12	80
5	Br_2	NaOH (1)	trace	97
6	NBS	$NaHCO_3$ (3.5)		96

[a] All reactions were carried out on 2.0 mmol of 8-methoxyquinaldine **1a** with 3 equiv of bromine for 10 min at room temperature. [b] Isolated yield. [c] 5-Bromo-8-methoxyquinaldine.

SCHEME 2. The Addition Reaction of 1-Methoxynaphthalene (1b)



We next wanted to study the effect of base on the reaction (Table 1). Treatment of 8-methoxyquinaldine **1a** with only 2 equiv of $NaHCO_3$ allowed some intermediate product, 5-bromo-8-methoxyquinaldine, **3a**, to remain (entry 2). Alternatively, treatment of **1a** with strong bases such as sodium methoxide or sodium hydroxide resulted in little to no formation of the addition product **2a** (entries 3–5). (It is likely that compound **2a** could be obtained in higher yield as a minor product by decreasing the amount of strong base used). Surprisingly, NaOH treatment also produced trace amounts of 5,7-dibromo-8-methoxyquinaldine. Last, in utilizing *N*-bromosuccinimide (NBS) as the brominating reagent, only product **3a** was observed, possibly due to the lower electrophilic reactivity of NBS toward aromatic systems. These results indicated that the reactivity of the base as well as that of the bromine reagent are very important in forming the addition adduct. Using strong base decreased the reactivity of bromine and resulted in elimination to form the substitution product. In addition, although some reports indicate that NBS can be used in the Ad_E reaction of olefins, it was insufficiently reactive in the case of aromatic systems.[7]

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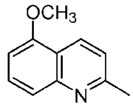
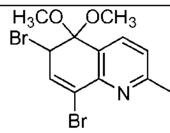
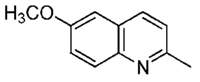
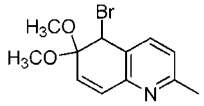
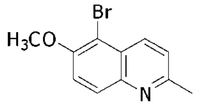
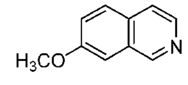
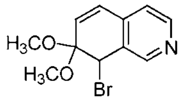
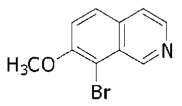
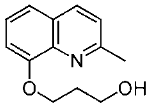
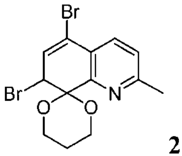
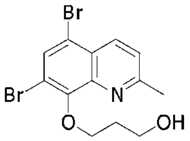
(5) (a) Choi, H. Y.; Lee, B. S.; Chi, D. Y.; Kim, D. J. *Heterocycles* **1998**, *48*, 2647–2652. (b) Yoon, E. Y.; Choi, H. Y.; Shin, K. J.; Yoo, K. H.; Chi, D. Y.; Kim, D. J. *Tetrahedron Lett.* **2000**, *41*, 7475–7480. (c) Yoo, K. H.; Yoon, E. Y.; Park, Y. Y.; Park, S. W.; Lee, C.-O.; Lee, W. G.; Chi, D. Y.; Kim, D. J. *Bull. Korean Chem. Soc.* **2001**, *22*, 1067–1068.

(6) Choi, H. Y.; Kim, D. W.; Chi, D. Y.; Yoon, E. Y.; Kim, D. J. *J. Org. Chem.* **2002**, *67*, 5390–5393.

(7) Sasaki, M.; Yudin, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 14242–14243.

TABLE 2. Bromoalkoxylation of Various Methoxy Bicyclic Aromatic Compounds under $NaHCO_3$–Methanol Conditions[a]

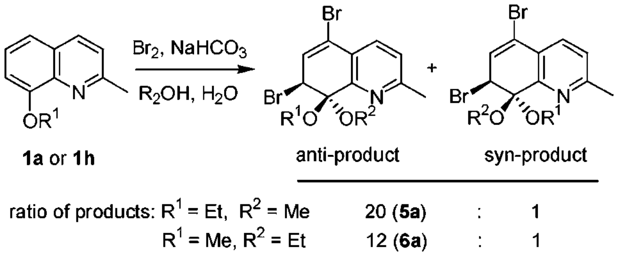
entry	compound	yield of product (%)[b]	
		addition adduct **2**	substitution adduct **3**
1	 **1c**	 **2c** (90)	-
2	 **1d**	 **2d** (47)	 **3d** (40)
3	 **1e**	 **2e** (75)	 **3e** (19)
4[c]	 **1f**	 **2f** (30)	 **3f** (12)

[a] Unless otherwise noted, all reactions were carried out under the same conditions as in Table 1, entry 1. [b] Isolated yield. [c] Acetonitrile was used as a solvent.

To check the generality of the reaction, we attempted the bromoalkoxylation of various bicyclic aromatic compounds under the same reaction conditions as Table 1, entry 1 (Table 2). The Ad_EAr reaction of 5-methoxyquinaldine **1c** (entry 1) proceeded well, giving the stable addition product **2c** in very high yield (90%). Alternatively, we obtained a mixture of both addition and substitution products when the β-methoxy compound, 6-methoxyquinaldine (**1d**), was used (entry 2). The ^1H NMR spectrum of **2d** showed a long-range coupling constant between H5 and H7 of 2.0 Hz, which is unusually large due to the planar W conformation of the four σ bonds. This suggests that the bromomethoxylated product exists in the same conformer as **2a**. TLC analysis indicates only 1.5 equiv of bromine are required to complete the reaction. Like the quinoline, the reaction of 7-methoxyisoquinoline **1e** gave product **2e** with similar results (entry 3). To study the effects of nonalcoholic solvents in the presence of additional nucleophiles, the hydroxy ether derivative **1f** was treated in acetonitrile (entry 4). The bromoalkoxylated spiro compound **2f** was isolated in moderate yield along with the dibromo byproduct, indicating the possibility of introducing various nucleophiles in conjunction with nonnucleophilic solvents for use in the Ad_EAr reaction.

The stereochemistry of the reaction was further investigated. Although it is well-known that many polar addition reactions of halogen electrophiles to alkenes take place with exclusive antistereochemistry, there are also many examples of syn additions.[8] The antiaddition can result from bridged bromonium ion intermediates and from very rapid capture of a carbocation intermediate by nucleophilic solvent. On the other hand, if the principal intermediate were an ion pair that collapsed faster than translocation about the anion, the syn addition could predominate. In the case of bromoalkoxylation, syn addition could be possible only when the brominating agent was hypobromite, which was reported to be formed from bromine in methanol under basic condition.[9] However, the mixture of both addition products could be obtained if the cationic intermediate were very stable.

SCHEME 3. The Reactions of 8-Ethoxyquinaldine and 8-Methoxyquinaldine



Therefore, the addition orientation can show the interpretation of reaction stereochemistry and mechanism. When methoxy compounds were treated in methanol solvent, we were unable to distinguish where each methoxy group came from. Therefore, the reactions of 8-ethoxyquinaldine (**1h**) in methanol and 8-methoxyquinaldine (**1a**) in ethanol were used in this study as shown in Scheme 3. Both reactions yielded a mixture of addition products, **5a** and **6a**, the major product being the antiaddition one. The structures of both products were confirmed by X-ray crystallography (Figure 2). The result elucidated that the alkoxylquinaldine reacted with bromine molecules to produce a stable cation intermediate and was finally attacked by a nucleophilic alkoxide, preferentially at the opposite side of the bromine group.

We have proposed a mechanism for this addition reaction (Scheme 4) in which the brominated reactant probably forms a cationic intermediate (σ complex),

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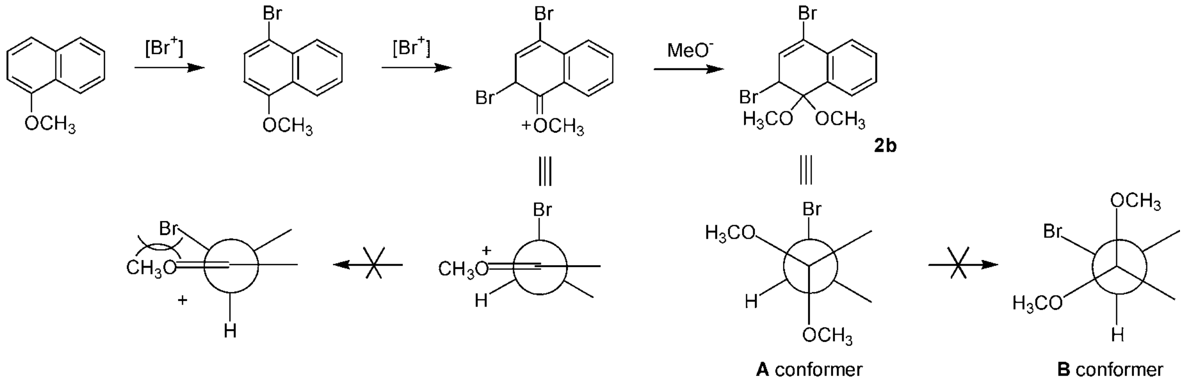
[8] Heasley, G. E.; Bower, T. R.; Dougharty, K. W.; Easdon, J. C. *J. Org. Chem.* **1980**, *45*, 5150–5155.

[9] (a) Dicks, P. F.; Glover, S. A.; Goosen, A.; McCleand C. W. *Tetrahedron* **1987**, *43*, 923–934. (b) Gervat, S.; Leonel, E.; Barraud, J.; Ratovelomanana, V. *Tetrahedron Lett.* **1993**, *34*, 2115–2118.

SCHEME 4. Mechanism of the Ad$_E$Ar Reaction



stabilized by the methoxy group. The formation of the stable complex possibly leads to either deprotonation–aromatization or nucleophilic capture. The aromatization from **2b** requires that the proton should be either anti-coplanar or syn-coplanar to methoxy. As the hydrogen occupies a gauche position with respect to the adjacent methoxy substituents in the **A** conformer, the change of conformation from **A** to **B** conformer (Scheme 4) might require much higher activation energy due to steric hindrance. These bulky moieties may hinder the solvent or other bases from assisting in proton removal, favoring either (a) regeneration of the reactant from the σ complex or (b) nucleophilic attack at the ipso position of the methoxy group, giving the kinetic addition adduct **2** as a racemic mixture. Although the formation of aromatic products is usually considered as under thermodynamic control, carbocation sequences often give products under kinetic control.[10] Moreover, the fused ring and the bulky group also make changing conformation impossible. The α-methoxy compounds **1a**–**c**,**f** yielded only addition adducts **2a**–**c**,**f**, whereas the β-methoxy compounds **1d**–**e** gave a mixture of both addition and substitution products, perhaps due to the acidity of the proton at the bromo position. The benzylic protons of the σ complex intermediates for **1d**–**e** should be easier to remove than the nonbenzylic protons of **1a**–**c**,**f**.

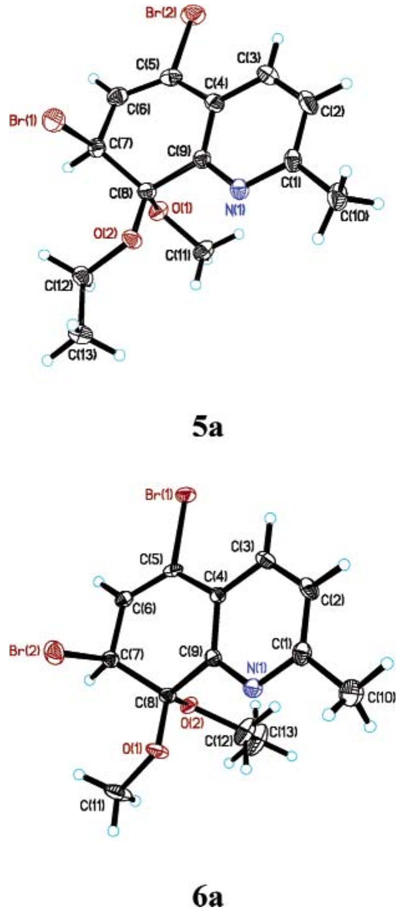


FIGURE 2. The X-ray structure of products **5a** and **6a**.

In summary, we have demonstrated a novel reaction and mechanism—electrophilic aromatic addition reaction (Ad$_E$Ar) at an aromatic H substituent position—for fused bicyclic aromatic compounds, as well as the first isolation of the corresponding addition adducts. These stable adducts should provide new tools for the functionalization of aromatic rings. The methoxy bicyclic aromatic system is a good example of the addition reaction of bromine and methoxide. Further studies regarding mechanism as well as applications of the addition products are currently underway in our laboratory.

Experimental Section

Typical Procedure for the Electrophilic Aromatic Addition Reaction. To the suspension of methoxy compound (2 mmol) and $NaHCO_3$ (3.5 or 1.75 equiv) in MeOH (6 mL) was added a solution of Br_2 (3.0 or 1.5 equiv) in MeOH (1.5 mL) with stirring at room temperature. After 5 min, water (3 mL) was added and the reaction was stirred for another 5 min. Then, water (30 mL) and Na_2SO_3 (0.32 g) were added. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). The residue was purified by flash column chromatography.

5,7-Dibromo-8,8-dimethoxy-7,8-dihydroquinaldine (2a). Yellowish crystalline solid, mp 142–143 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.69 (s, 3H), 3.00 (s, 3H), 3.54 (s, 3H), 4.87 (d, $J = 7.0$ Hz, 1H), 6.68 (d, $J = 7.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.1, 47.1, 48.9, 52.0, 98.4, 123.2, 124.0, 125.1, 129.2, 135.9, 150.4, 158.8; MS (EI) 365 (M^+), 363 (M^+), 361 (M^+), 330, 254, 252 (100), 250, 237, 222, 203, 188, 174, 157, 142, 128, 115, 102, 86. Anal. Calcd for $C_{12}H_{13}Br_2NO_2$: C, 39.70; H, 3.61; N, 3.86. Found: C, 39.74; H, 3.66; N, 3.61.

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(10) de la Mare, P. B. *Acc. Chem. Res.* **1974**, *7*, 361–368.

2,4-Dibromo-1,1-dimethoxy-1,2-dihydronaphthalene (2b). Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.88 (s, 3H), 3.44 (s, 3H), 4.82 (d, J = 7.0 Hz, 1H), 6.65 (d, J = 7.0 Hz, 1H), 7.40−7.66 (m, 2H), 7.67−7.79 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 47.4, 48.5, 51.3, 98.6, 125.3, 127.3, 128.2, 129.0, 129.3, 129.6, 131.0, 132.5; MS (CI) 350 (M$^+$), 348 (M$^+$), 346 (M$^+$), 332, 330, 328, 318, 316, 314, 303, 301, 299, 275, 273, 271, 238, 236, 223, 221, 195, 193. Anal. Calcd for $C_{12}H_{12}Br_2O_2$: C, 41.41; H, 3.48. Found: C, 41.46; H, 3.85.

6,8-Dibromo-5,5-dimethoxy-5,6-dihydroquinaldine (2c). Colorless crystalline solid, mp 151−152 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.64 (s, 3H), 2.89 (s, 3H), 3.45 (s, 3H), 4.80 (d, J = 7.0 Hz, 1H), 6.94 (d, J = 7.0 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.8, 46.6, 48.7, 51.4, 99.0, 123.2, 126.0, 127.0, 132.6, 135.6, 147.2, 159.4; MS (CI) 366 (M$^+$ + 1), 364 (M$^+$ + 1), 362 (M$^+$ + 1), 332, 282, 254, 252 (100). Anal. Calcd for $C_{12}H_{13}Br_2NO_2$: C, 39.70; H, 3.61; N, 3.86. Found: C, 39.92; H, 4.01; N, 3.69.

5-Bromo-6,6-dimethoxy-5,6-dihydroquinaldine (2d). Off-white solid, mp 67−68 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.23 (s, 3H), 3.42 (s, 3H), 5.17 (d, J = 2.2 Hz, 1H), 6.16 (dd, J = 10.2, 2.2 Hz, 1H), 6.83 (d, J = 10.6 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.5, 48.4, 49.4, 51.4, 98.9, 122.6, 128.9, 132.0, 132.9, 136.3, 150.0, 158.7; MS (EI) 285 (M$^+$), 283 (M$^+$), 253, 251, 204, 173, 158, 130, 103, 77, 63, 51; HRMS (EI) calcd for $C_{12}H_{14}BrNO_2$ (M$^+$) 283.0208, found 283.0206.

8-Bromo-7,7-dimethoxy-7,8-dihydroisoquinoline (2e). Yellowish liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.20 (s, 3H), 3.44 (s, 3H), 5.24 (d, J = 1.4 Hz, 1H), 6.14 (dd, J = 10.0, 1.4 Hz, 1H), 6.67 (d, J = 10.0 Hz, 1H), 7.09 (d, J = 5.2 Hz, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.57 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.6, 48.3, 51.3, 98.8, 121.4, 128.1, 130.9, 133.7, 137.7, 149.3, 150.8; MS (EI) 271 (M$^+$), 269 (M$^+$), 240, 238, 225, 223, 190, 175, 159, 144, 116, 89, 63; HRMS (EI) calcd for $C_{11}H_{12}BrNO_2$ (M$^+$) 269.0051, found 269.0051.

5′,7′-Dibromo-7′*H*-spiro[1,3-dioxane-2,8′-quinaldine] (2f). Colorless crystalline solid, mp 138−139 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71−2.00 (m, 2H), 2.66 (s, 3H), 3.70−3.91 (m, 2H), 4.11−4.19 (m, 1H), 5.02 (d, J = 6.6 Hz, 1H), 5.10−5.22 (m, 1H), 6.61 (d, J = 7.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.8, 25.1, 48.9, 63.0, 95.3, 123.6, 123.9, 125.1, 128.6, 135.9, 152.7, 158.5; MS (CI) 378, 376, 374, 298, 296, 294, 240, 238. Anal. Calcd for $C_{13}H_{13}Br_2NO_2$: C, 41.63; H, 3.49; N, 3.73. Found: C, 41.97; H, 3.88; N, 3.62.

8-(3-Hydroxypropanoxy)quinaldine (1f). To solution of 8-hydroxyquinaldine (1.59 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in acetone (30 mL) was added 4-bromopropanol and the reaction was refluxed for 24 h. The solution was poured into water (50 mL), then extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with water and brine and dried (Na_2SO_4). After removal of solvent in vacuo, the residue was purified by flash column chromatography (60% EtOAc−hexane), giving **1f** (1.82 g, 84%) as white foam: mp 106 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (m, 2H), 2.74 (s, 3H), 3.99 (t, J = 5.4 Hz, 2H), 3.99 (t, J = 6.0 Hz, 2H), 5.01 (br s, 1H), 7.12 (dd, J = 5.8, 3.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.32−7.39 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.4, 32.2, 61.6, 70.9, 112.8, 120.9, 122.9, 126.0, 128.0, 136.5, 140.5, 154.6, 158.7; MS (CI) 246 (M$^+$ + 29), 218 (M$^+$ + 1), 200, 172, 144. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.92; H, 7.26; N, 6.09.

(*S*,*R*)- and (*R*,*S*)-5,7-Dibromo-8-ethoxy-8-methoxy-7,8-dihydroquinaldine (5a). Colorless crystalline solid, mp 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 2.64 (s, 3H), 2.97 (s, 3H), 3.76 (q, J = 7.1 Hz, 2H), 4.86 (d, J = 6.8 Hz, 1H), 6.64 (d, J = 6.8 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 24.6, 47.6, 51.6, 56.5, 98.0, 122.9, 123.5, 124.6, 128.9, 135.5, 150.1, 158.6; MS (EI) 379 (M$^+$, 11), 377 (M$^+$, 24), 375 (M$^+$, 12), 332, 316, 290, 268, 252 (100), 239, 223, 210, 188. Anal. Calcd for $C_{13}H_{15}Br_2NO_2$: C, 41.41; H, 4.01; N, 3.78. Found: C, 41.56; H, 4.38; N, 3.58.

(*S*,*S*)- and (*R*,*R*)-5,7-Dibromo-8-ethoxy-8-methoxy-7,8-dihydroquinaldine (6a). Colorless crystalline solid, mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3H), 2.67 (s, 3H), 2.84−2.88 (m, 1H), 3.52 (s, 3H), 3.58−3.62 (m, 1H), 4.86 (d, J = 7.2 Hz, 1H), 6.67 (d, J = 6.8 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 24.7, 47.1, 48.6, 59.8, 97.8, 122.6, 123.8, 124.9, 129.2, 135.6, 150.6, 158.5; MS (EI) 379 (M$^+$, 5), 377 (M$^+$, 10), 375 (M$^+$, 5), 330, 316, 290, 268, 252 (100), 237, 223, 210, 202, 188. Anal. Calcd for $C_{13}H_{15}Br_2NO_2$: C, 41.41; H, 4.01; N, 3.78. Found: C, 41.46; H, 4.37; N, 3.59.

Acknowledgment. This work was supported by the Real Time Molecular Imaging Project of KISTEP (2004-02156) in Korea and we thank Professor Peter Beak and Ms. Lynne Miller-Deist for helpful discussions. High resolution mass spectra were carried out at the Korea Basic Science Institute (Daegu, Korea). This work is dedicated to Professor John A. Katzenellenbogen of the University of Illinois at Urbana−Champaign on the occasion of his 60th birthday (May 10, 2004).

Supporting Information Available: Experimental procedure of starting materials and characterization data of the rest of the compounds and crystallographic data collection parameters for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048297X