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Facile and Regioselective Dealkylation of Alkyl Aryl Ethers Using Niobium(V) Pentachloride

Yukinori Sudo,[a] Shigeru Arai,*[a] and Atsushi Nishida*[a]

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A simple and facile method for the cleavage of carbon–oxygen bonds promoted by niobium pentachloride(V) is described. Excellent yields and regioselectivities were observed with various alkyl aryl ethers to give the phenols. NMR studies revealed the formation of monoaryloxy niobium salt(V), and a neighboring-group effect may play a significant role in the regioselectivity.

Introduction

Ever since Pedersen and co-workers reported the $NbCl_3$(DME) complex,[1] low-valence niobium reagents have been attractive tools in organic synthesis due to their unique reactivities. For example, they are known to react with carbon–nitrogen,[1,2] carbon–oxygen[3,4] and carbon–carbon multiple bonds[5,6] to give 1,2-dianion or radical species. On the other hand, recent studies of Nb^V have focused on organic transformations in carbon–carbon bond formation which are typical Lewis acid-mediated reactions,[7–9] except for unique reactions such as cyclopropane formation[10] and dealkylative acylation.[11] We were interested in the strong Lewis acidity of Nb^V, and started to investigate its unique reactivity. In this article, we describe in detail new aspects of Nb^V as a Lewis acid through cleavage of a carbon–oxygen bond.[12]

Results and Discussion

The removal of alkyl groups from alkyl aryl ethers is one of the most fundamental reactions in organic synthesis, and strong Lewis acids (BBr_3[13,14] and TMSI[15,16]) and nucleophiles (EtSNa[17,18] and $NaN(TMS)_2$[19]) have been used as promoters. We anticipate that $NbCl_5$ may also promote C–O bond cleavage due to its strong Lewis acidity. First, we investigated the monodemethylation of **1a** using various Lewis acids to give mono-methyl ether **2a**, which is an important chiral ligand for asymmetric synthesis.[20] These reactions in the presence of $AlCl_3$[21] and $TiCl_4$ under reflux conditions in toluene were quite unsuccessful even after 5 h despite their strong Lewis acidity, and **1a** was recovered in yields of 97 and 96%, respectively, as shown in Table 1 (Entries 1 and 2). When metal chlorides in groups 5 and 6, such as $MoCl_5$, WCl_6 and $TaCl_5$, were tested under similar conditions, they were ineffective and gave **2a** in less than 18% yield (Entries 3–5). On the other hand, dealkylation with $NbCl_5$ was completed within 30 min under similar conditions to give **2a** in 99% yield, which shows its strong Lewis acidity (Entry 6). BBr_3, a widely-used reagent for demethylation, also promoted the reaction to give **2a** in 90% yield, though **3** was obtained in 9% yield even in the best conditions (at –78 °C) (Entry 7). Compared to BBr_3, $NbCl_5$ is easier to handle and less sensitive to moisture.

Next, the reactions of various dialkyl ethers with $NbCl_5$ (1.1 equiv.) were examined, as shown in Table 2. Diethyl ether **1b** gave the corresponding mono-ethyl ether **2b** in 91% yield under similar conditions together with **3** in 6% yield (Entry 1). Since **1b** was more reactive than **1a**, the reaction was accomplished in CH_2Cl_2 under reflux to give **2b** in quantitative yield (Entry 2). Dibenzyl ether **1c** was highly reactive and selective mono-dealkylation was achieved at –78 °C to give **2c** in 61% yield with recovery of **1c** (35%) (Entry 3). To complete the reaction, 1.5 equiv. of $NbCl_5$ was necessary to give **2c** in 87% yield (Entry 4). In the case of **1d**, both MPM ethers were quickly cleaved (Entry 5).

We next studied the discrimination of alkyl groups, as shown in Table 3. For example, treatment of ethyl methyl ether **4** with $NbCl_5$ (1.1 equiv.) under optimized conditions gave **2a** in 91% yield together with **2b** in 9% yield. Although BBr_3, like $NbCl_5$, was effective in the monodemethylation of **1a** under the best conditions (1.1 equiv. of BBr_3 at –78 °C), its selectivity in the reaction with **4** was lower, and both **2a** and **2b** were obtained in respective yields of 56 and 23% along with the recovery of **4** in 20% yield. A lower selectivity was also observed (**2a**/**2b**/**3** = 19:13:60)

[a] Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan
E mail: arai@p.chiba-u.ac.jp

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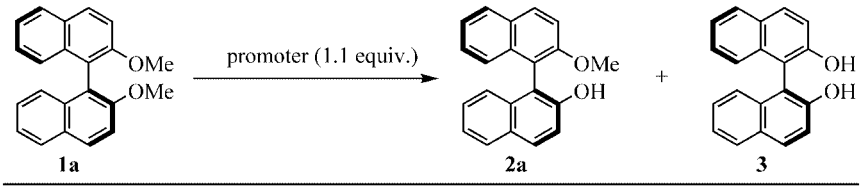
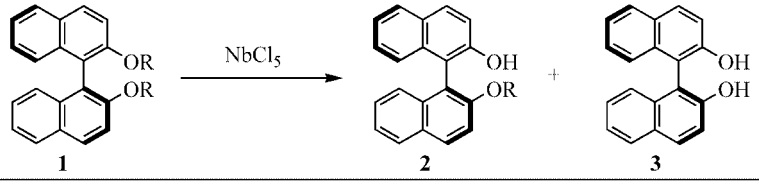
Table 1. Monodemethylation of **1a** with various Lewis acids.



1a **2a** **3**

entry	promoter	conditions	**2a** (%)	**3** (%)	**1a** (%)
1	$AlCl_3$	PhMe, reflux, 5 h	trace	1	97
2	$TiCl_4$	PhMe, reflux, 5 h	trace	2	96
3	$MoCl_5$	PhMe, reflux, 5 h	0	2	98
4	WCl_6	PhMe, reflux, 9 h	18	18	60
5	$TaCl_5$	PhMe, reflux, 5 h	trace	trace	99
6	$NbCl_5$	PhMe, reflux, 0.5 h	99	1	0
7	BBr_3	CH_2Cl_2, –78 °C, 7 h	90	9	0

Table 2. Dealkylation of **1b–d** derived from BINOL.

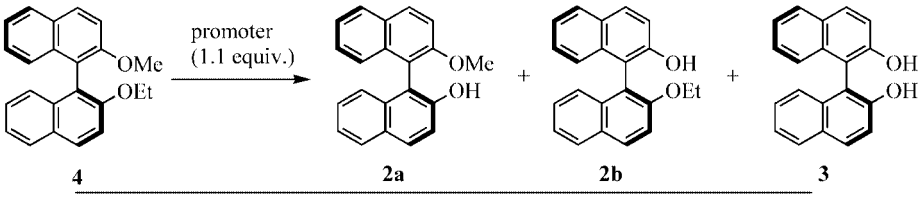


1 **2** **3**

entry	**1**	NbCl (equiv.)	conditions	**2** (%)	**3** (%)
1	**1b**: R = Et	1.1	PhMe, reflux, 0.5 h	**2b**: 91	6
2	**1b**: R = Et	1.1	CH_2Cl_2, reflux, 7 h	**2b**: quant.	0
3	**1c**: R = Bn	1.1	PhMe, –78 °C, 3 h	**2c**: 61[a]	4
4	**1c**: R = Bn	1.5	PhMe, –78 °C, 3 h	**2c**: 87	8
5	**1d**: R = MPM	1.1	PhMe, –78 °C, 1.5 h	**2d**: 0	91

[a] **1c** was recovered in 35% yield.

Table 3. Differentiation between ethyl and methyl ether of **4**.



4 **2a** **2b** **3**

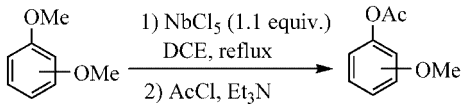
promoter	conditions	**2a** (%)	**2b** (%)	**3** (%)
$NbCl_5$	DCE, reflux, 0.5 h	91	9	0
BBr_3	CH_2Cl_2, –78 °C, 24 h	56	23	trace

at higher temperature (–78 to –20 °C for 26 h). These results demonstrate the synthetic utility and unique character of $NbCl_5$.

Further investigation using the isomers of dimethoxybenzenes with $NbCl_5$ gave interesting results, as shown in Table 4. For example, *o*-dimethoxybenzene **5a**, which could be a bidentate ligand for Nb atom, reacted immediately with $NbCl_5$ to give the desired mono-demethylated product,[22] which was isolated as the corresponding acetate **6a** (91%). On the other hand, both **5b** and **5c** were less reactive and gave the desired products **6b** and **6c** in respective yields of 17 and 26% after a longer reaction time.

To obtain further information on this chelation effect on dealkylation, 1,2-dialkoxybenzene derivatives were examined (Scheme 1). 3-Methyl-1,2-dimethoxybenzene **7a** reacted with $NbCl_5$ in dichloroethane (DCE) at room temp. Due to the high volatility of the corresponding phenols, **8a** and **9a** were isolated in quantitative yield in a ratio of 93:7 after mesylation, as shown in Scheme 1. In the case of diethyl ether **7b**, perfect selectivity was observed and **8b** was

Table 4. Mono-dealkylation of 1,*n*-dimethoxybenzenes.



5a–c **6a–c**

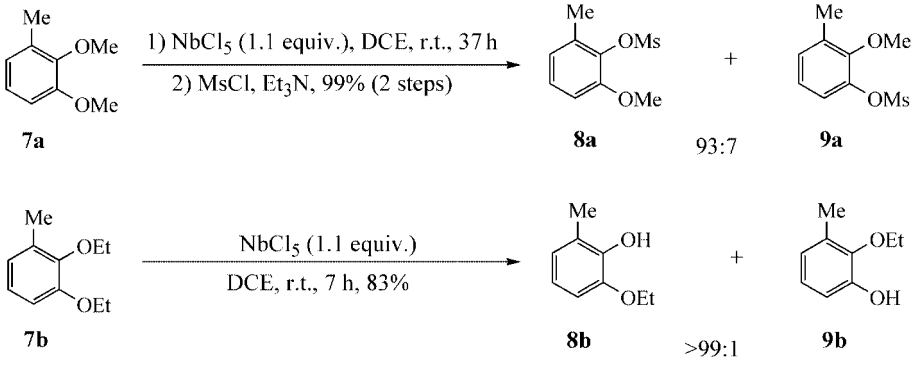
entry	substrate	time (h)	yield of **6** (%)
1	**5a**: 2-OMe	1.3	**6a**: 91
2	**5b**: 3-OMe	22	**6b**: 17
3	**5c**: 4-OMe	24	**6c**: 26

isolated in 83% yield. On the other hand, the use of BBr_3 (1.1 equiv.) with **7a** in CH_2Cl_2 at –78 to –20 °C (14 h) followed by mesylation gave **8a** and the corresponding dimesylate in respective yields of 61 and 29%. These results suggest that $NbCl_5$ can influence the steric environment, and dealkylates hindered alkoxy groups. Since the reported assignments of the regioisomers of methoxycresol were ambiguous,[19] dealkylated products were converted to known compounds to confirm their structure, as outlined in Scheme 2. The alkoxyaromatic compounds **7a** and **8b** were transformed to the corresponding *m*-alkoxytoluenes **11a** and **11b** by reduction using a Pd catalyst via triflates **10a** and **10b**, respectively.[23] These products were identified using authentic samples prepared from *m*-cresol.

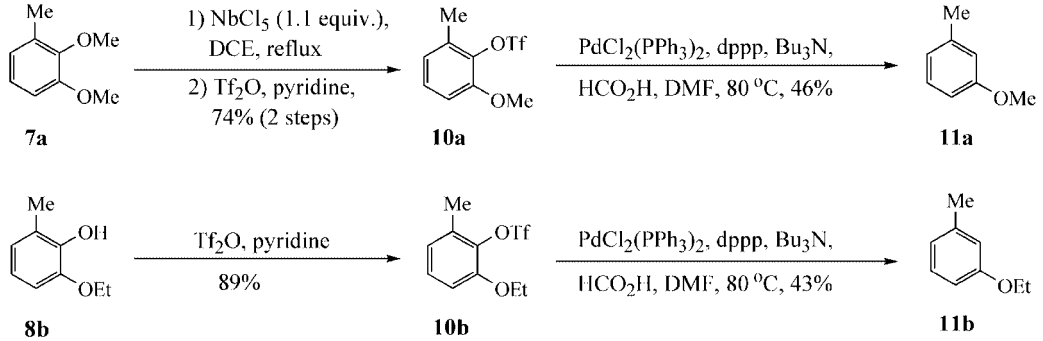
3-Substituted 1,2-dimethoxybenzenes **7c–g** were examined to evaluate the scope and limitations of this reaction. For example, the 3-methoxy derivative **7c** smoothly underwent mono-demethylation to give the corresponding phenol in which the hindered methyl group was predominantly removed (**8c/9c** = 96:4, Entry 1). The substrate **7d**, which contains the electron-withdrawing CO_2Me group, was also transformed to the corresponding phenol **8d** in 91% yield (Entry 2). 3-Fluoro derivative **7e** was successfully converted to **8e** with satisfactory yield and selectivity (Entry 3). In the reaction of 4-substituted 1,2-dialkoxybenzenes such as **7f** and **7g**, dealkylation of the reaction proceeded smoothly to give two isomers of alkoxyphenols, without any regioselectivity (Entries 4 and 5). These results are summarized in Table 5. All of the products shown in Table 5 were assigned by comparison with reported values in the NMR spectra.[24]

The reaction of 2-substituted methoxybenzenes with $NbCl_5$ was useful for testing the ability of functional groups to chelate to $NbCl_5$. Two examples are shown in Table 6. *o*-Methoxybenzoate **12a** was converted into the corresponding phenol, and subsequent acetylation gave **13a** in 84% yield, although the reaction was slower than **7d** (Entry 1). In the case of 2-fluoroanisole (**12b**), the reaction did not proceed at all under similar conditions (Entry 2). These results suggest that **12a** may act as a bidentate ligand to promote dealkylation.

To clarify the interaction of $NbCl_5$ with a bidentate ether ligand, we followed the demethylation of **5a** by NMR

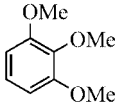
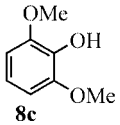
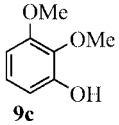
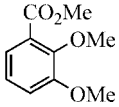
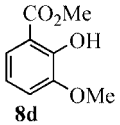
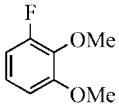
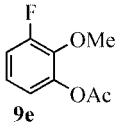
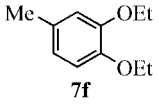
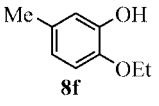
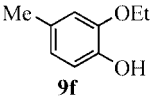
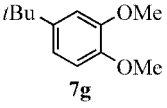
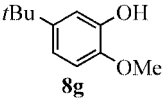
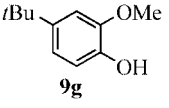


Scheme 1. Dealkylation of **7a** and **7b**.



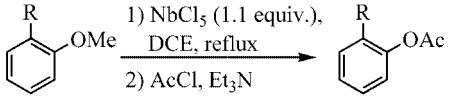
Scheme 2. Transformation of **7a** and **8b**.

Table 5. Dealkylation of substituted 1,2-dimethoxybenzenes.[a]

entry	substrate	conditions	products		results
1	 **7c**	reflux, 1 h	 **8c**	 **9c**	92% **8c**/**9c** = 94:6
2	 **7d**	reflux, 1 h	 **8d**		91%
3	 **7e**	reflux, 1.5 h	 **8e**	 **9e**	79%[b] **8e**/**9e** = 96:4
4	 **7f**	r.t., 27 h	 **8f**	 **9f**	92% **8f**/**9f** = 50:50
5	 **7g**	reflux, 1.2 h	 **8g**	 **9g**	92% **8g**/**9g** = 50:50

[a] All reactions were carried out in DCE in the presence of $NbCl_5$ (1.1 equiv.). [b] Chemical yield was determined after conversion to the corresponding acetates (2 steps).

Table 6. Dealkylation of 2-substituted methoxybenzenes.



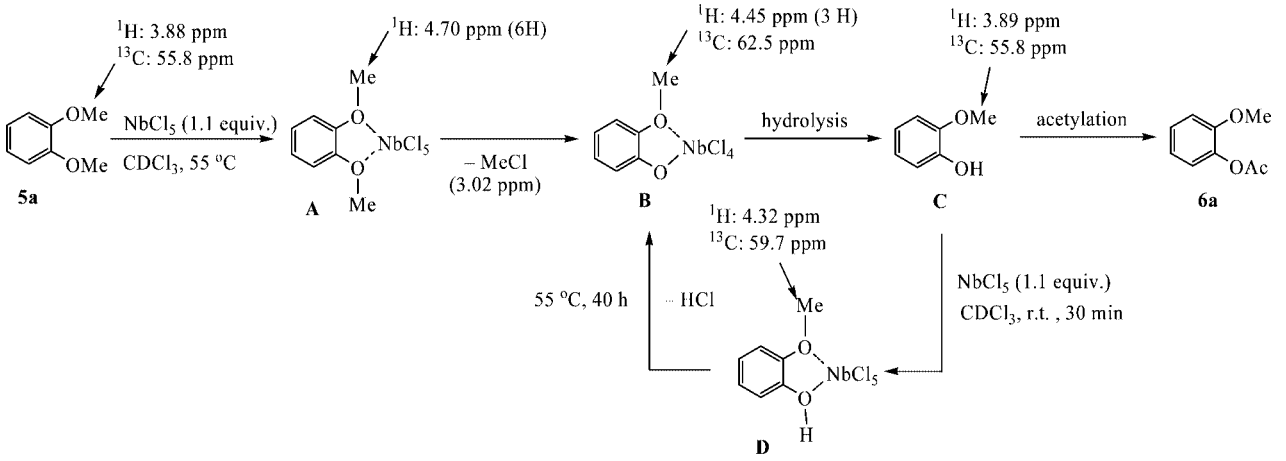
12 **13**

entry	substrate	time (h)	yield of **13** (%)
1	**12a**: R = CO_2Me	6	**13a**: 84
2	**12b**: R = F	24	**13b**: 0

(Scheme 3). Treatment of **5a** with $NbCl_5$ in $CDCl_3$ at 55 °C showed three new singlet signals at δ = 4.70, 4.45, and 3.02 ppm, together with a peak at δ = 3.88 ppm (**5a**) after 15 min. After 8 h, all the peaks of **5a** completely disappeared. The signal at δ = 4.70 ppm disappeared completely after 16 h at 55 °C, and only the signal at δ = 4.45 ppm remained. Hydrolysis of the mixture followed by acetylation gave **6a** in 84% yield. The same signal (δ = 4.70 ppm) was also observed in a mixture of $NbCl_5$ and **5a** at room temperature, and subsequent hydrolysis of the mixture with heating led to the recovery of **5a**. Thus, these observations indicate the formation of symmetrical niobium complex **A** as a reactive intermediate in which the two oxygen atoms of the MeO groups act as Lewis bases. The two additional peaks at δ = 4.45 and 3.02 ppm could be assigned to the oxoniobium salt **B** and methyl chloride, respectively. The ^{13}C NMR spectrum after 16 h also supported the formation of asymmetrical niobium salt **B**, in which six nonequivalent signals observed at 111.9–151.3 ppm were assigned to be the benzene ring. The niobium salt **B** was stable under the reaction conditions, and no significant change was observed in either the ^1H or ^{13}C NMR spectrum even after 24 h at 55 °C. On the other hand, treatment of **C** with $NbCl_5$ in $CDCl_3$ at room temperature for 30 min gave a new peak at δ = 4.32 ppm. The signals of **C** completely disappeared after 40 h at 55 °C, and the formation of salt **B** was observed. The initial signals can be assigned to complex **D**, and subsequent elimination of HCl gave **B**.

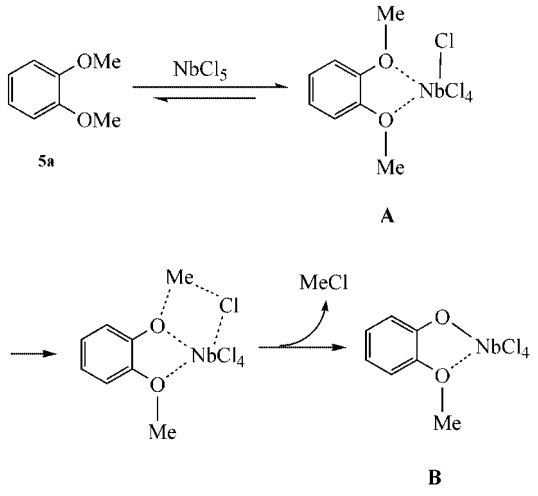
A plausible mechanism of this demethylation is shown in Scheme 4. Complexation of $NbCl_5$ to *o*-dimethoxybenzene **5a** is very rapid and strongly favors complex **A**. In considering the reactivity of the alkyl ethers in Table 2 (–O–MPM >> –O–Bn > –O–Et > –O–Me), S_N1-type substitution occurred in the cleavage of the ether linkage. The resulting niobium salt **B** is inactive as a Lewis acid to promote further dealkylation, except for the reaction of the MPM ether.

In conclusion, we have demonstrated an efficient and selective methodology for C–O bond cleavage promoted by $NbCl_5$ via chelation due to its strong oxophilicity, and these observations should offer new insights into niobium chemistry. Further investigation on a possible application in organic synthesis is underway.



	^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C) δ values	^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ values
5a	3.88 (s, 6H), 6.87-6.94 (m, 4H)	55.8, 111.5, 120.9, 149.2
B	4.45 (s, 3H), 6.92-6.95 (m, 1H), 7.17-7.26 (m, 3H)	62.5, 111.9, 115.2, 124.6, 128.4, 148.3, 151.3
C	3.89 (s, 3H), 5.71 (s, 1H), 6.82-6.94 (m, 4H)	55.8, 110.7, 114.5, 120.1, 121.4, 145.6, 146.5
D	4.32 (s, 3H), 6.82-6.94 (m, 4H)	59.7, 112.3, 118.4, 122.4, 127.5, 151.6, 152.5

Scheme 3. NMR study of demethylation using **5a**.



Scheme 4. A plausible mechanism for the $NbCl_5$-promoted dealkylation.

Experimental Section

General Remarks: All reactions were performed with dry solvents, and reagents were purified by the usual methods. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with silica gel (Fuji Silysia, PSQ-60B). IR spectra were recorded with a JASCO FT/IR-230 Fourier transform spectrophotometer. NMR spectra were recorded with a JEOL-JMN-Alpha-400 spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, and calibrated using residual undeuterated solvent as an internal reference. Mass spectra were measured by JEOL JMS-AX500 (for LR-MS) and JEOL JMS-HX110 (for HR-MS) mass spectrometers.

Synthesis of 2,2′-Bis(4-methoxybenzyloxy)-1,1′-binaphthyl (1d): (±)-BINOL was treated under standard *O*-alkylation conditions (K_2CO_3, MPMCl in acetone, reflux for 48 h) to give **2d** as a white powder (94% yield). M.p. 138–140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.68 (s, 6 H), 4.93 (d, J = 12.0 Hz, 2 H), 4.97 (d, J = 12.0 Hz, 2 H), 6.59 (d, J = 8.4 Hz, 4 H), 6.85 (d, J = 8.8 Hz, 4 H), 7.15–7.22 (m, 4 H), 7.32 (dt, J = 1.6, 7.2 Hz, 2 H), 7.40 (d, J = 9.2 Hz, 2 H), 7.85 (d, J = 8.4 Hz, 2 H), 7.90 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.1, 71.1, 113.4, 116.4, 121.0, 123.6, 125.5, 126.2, 127.8, 128.4, 129.1, 129.4, 129.5, 134.1, 154.1, 158.8 ppm. IR (KBr): $\tilde{\nu}$ = 1613, 1587, 1512, 1247, 1172, 1037, 808 cm^{-1}. MS (FAB): m/z = 526 (M^+). HRMS (FAB): calcd. for $C_{36}H_{30}O_4$, 526.2144; found 526.2139.

General Procedure for Demethylation Promoted by $NbCl_5$. Synthesis of 2a: To a mixture of **1a** (40 mg, 0.13 mmol) and $NbCl_5$ (38 mg, 0.14 mmol) under argon was added toluene (1.3 mL), and the mixture was heated under reflux for 0.5 h. After the reaction was quenched by the addition of water (1 mL) at room temperature, the mixture was extracted with AcOEt (5 mL, 3 times). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. Subsequent flash column chromatography on silica gel (hexane/AcOEt, 8:1) gave the desired product **2a**[20] as a white amorphous solid (37.8 mg, 99%).

Synthesis of 8a: To a suspension of $NbCl_5$ (160 mg, 0.59 mmol) in dichloroethane (5.4 mL) was added **7a** (80 μL, 0.54 mmol) at room temperature. After this mixture was stirred for 37 h at room temp., the reaction was quenched with water (3 mL), and the resulting mixture was extracted with CH_2Cl_2 (5 mL, 3 times). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. After the organic solvents were removed in vacuo, the resulting crude product was mesylated under standard conditions and purified by column chromatography on silica gel (hexane/AcOEt, 8:1) to give **8a**[25] (107.4 mg, 92%) and **9a** (7.6 mg, 7%) as colorless oils.

(*S*)-2-Ethoxy-2′-methoxy-1,1′-binaphthyl (4): Compound **2a** (90 mg, 0.30 mmol) was treated under standard *O*-alkylation conditions (K_2CO_3, EtBr, NaI in acetone, reflux for 48 h) to give **4** as a white powder (56.2 mg, 0.17 mmol, 57%). M.p. 118–119 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (t, J = 7.2 Hz, 3 H), 3.75 (s, 3 H), 3.96–4.08 (m, 2 H), 7.10–7.44 (m, 8 H), 7.84–7.96 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.0, 56.7, 65.3, 114.0,

116.0, 119.7, 120.5, 123.4, 123.5, 126.1, 126.2, 127.8, 127.9, 129.1, 129.20, 129.22, 129.3, 134.0, 134.1, 154.3, 154.9 ppm. IR (KBr): $\tilde{\nu}$ = 1618, 1590, 1507, 1459, 1354, 1237, 1096, 1062, 809 cm^{-1}. LRMS (FAB): *m*/*z* = 328 (M^+). HRMS (FAB): calcd. for $C_{23}H_{20}O_2$, 328.1463; found 328.1451. $[\alpha]_D^{24}$ –55.5 (*c* = 1.0, $CHCl_3$).

2-Methoxy-6-methylphenyl Methansulfonate (8a): Colorless oil, ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3 H), 3.17 (s, 3 H), 3.85 (s, 3 H), 7.04 (dd, *J* = 8.0, 8.0 Hz, 1 H), 7.12–7.20 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.8, 37.9, 60.9, 122.1, 124.3, 130.0, 133.4, 142.7, 150.1 ppm. IR (neat): $\tilde{\nu}$ = 3022, 2939, 1482, 1426, 1367, 1267, 1240, 1213, 1175 cm^{-1}. MS (FAB): *m*/*z* = 217 [M + H]$^+$. HRMS(FAB): calcd. for $C_9H_{12}O_4S$, 216.0456; found 216.0467.

2-Methoxy-3-methylphenyl Methansulfonate (9a): Colorless oil, ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.38 (s, 3 H), 3.31 (s, 3 H), 3.86 (s, 3 H), 6.81–6.85 (m, 2 H), 7.13 (dd, *J* = 8.0, 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.9, 39.6, 55.8, 110.0, 123.1, 127.2, 134.0, 137.9, 151.6 ppm. IR (neat): $\tilde{\nu}$ = 3022, 2941, 2836, 1611, 1482, 1359, 1307, 1278 cm^{-1}. MS (FAB): *m*/*z* = 217 [M + H]$^+$. HRMS(FAB): calcd. for $C_9H_{12}O_4S$, 216.0456; found 216.0467.

Synthesis of 2-Methoxy-6-methylphenyl Trifluoromethanesulfonate (10a): To a suspension of $NbCl_5$ (391 mg, 1.46 mmol) in dichloroethane (13 mL) was added **7a** (200 mg, 1.31 mmol) at room temperature. After this mixture was stirred for 1 h under reflux conditions, the reaction was quenched with water (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (5 mL, 3 times). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. After the organic solvents were removed in vacuo, the resulting crude product was dissolved in CH_2Cl_2 (13 mL). To this solution were added Tf_2O (0.66 mL, 3.94 mmol) and pyridine (0.32 mL, 3.94 mmol) at room temperature, and the mixture was stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (5 mL) and the mixture was extracted with CH_2Cl_2 (5 mL, 3 times). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt, 15:1) to give **10a** (262 mg, 74%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.36 (s, 3 H), 3.88 (s, 3 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 7.19 (dd, *J* = 8.4, 8.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.3, 56.0, 110.4, 118.7 (q, *J* = 318.4 Hz), 123.1, 128.2, 132.1, 137.8, 151.3 ppm. IR (neat): $\tilde{\nu}$ = 1482, 1413, 1199, 1130, 1091, 1077, 880 cm^{-1}. MS (EI): *m*/*z* = 270 (M^+). HRMS (EI): calcd. for $C_9H_9F_3O_4S$, 270.0174; found 270.0186.

Transformation of 10a to *m*-Cresol (11a): To a solution of **10a** (243 mg, 0.9 mmol) in DMF (3 mL) and formic acid (0.1 mL, 2.7 mmol) were added $PdCl_2(PPh_3)_2$ (38 mg, 54 μmol, 5 mol-%), dppp (56 mg, 0.13 mmol) and tributylamine (0.90 mL, 3.78 mmol) at room temperature. After this mixture was stirred for 8 h at 80 °C, the reaction was quenched with water (10 mL) and the resulting mixture was extracted with Et_2O (5 mL, 3 times). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash column chromatography (hexane/AcOEt, 50:1) on silica gel to give **11a** (50.3 mg, 0.41 mmol, 46%) as a colorless oil. Compounds **10b** and **11b** were also prepared from **8b**[25] by a procedure similar to that shown in Scheme 3.

2-Ethoxy-6-methylphenyl Trifluoromethanesulfonate (10b): ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (t, *J* = 6.8 Hz, 3 H), 4.10 (q, *J* = 6.8 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 7.16 (dd, *J* = 8.4, 8.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 16.3, 64.7, 110.0, 118.6 (q, *J* = 318.4 Hz), 122.8, 128.1, 132.0, 137.9, 150.6 ppm. IR (neat): $\tilde{\nu}$ =1473, 1414, 1199, 1132, 1086, 1072, 883 cm^{-1}. MS (EI): *m*/*z* = 284 (M^+). HRMS (EI): calcd. for $C_{10}H_{11}F_3O_4S$, 284.0330; found 284.0349.

Synthesis of 8e and 9e: To a suspension of $NbCl_5$ (168 mg, 0.62 mmol) in dichloroethane (4.7 mL) was added a solution of **7e** in dichloroethane (88 mg, 0.56 mmol, 0.9 mL) at room temperature. After this mixture was stirred for 1.5 h under reflux conditions, the reaction was quenched with water (2 mL) and the resulting mixture was extracted with CH_2Cl_2 (5 mL, 3 times). The combined organic layers were washed with brine (5 mL) and dried with Na_2SO_4. After the organic solvents were removed in vacuo, the resulting crude product was dissolved in dichloromethane (5.6 mL). To this solution were added NEt_3 (157 μL, 1.13 mmol) and AcCl (80 μL, 1.13 mmol) at room temperature, and the mixture was stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and the mixture was extracted with CH_2Cl_2 (5 mL, 3 times). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4, and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt, 12:1) to give **8e** (79.3 mg, 76%) and **9e** (2.7 mg, 3%) as colorless oils.

2-Fluoro-6-methoxyphenyl Acetate (8e): ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.35 (d, *J* = 0.4 Hz, 3 H), 3.83 (s, 3 H), 6.73–6.79 (m, 2 H), 7.10–7.16 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2, 56.3, 107.6 (d, *J* = 2.4 Hz), 108.5 (d, *J* = 19.7 Hz), 126.3 (d, *J* = 9.8 Hz), 127.8 (d, *J* = 14.8 Hz), 155.2 (d, *J* = 246.8 Hz), 152.9 (d, *J* = 4.1 Hz), 168.1 ppm. IR (neat): $\tilde{\nu}$ = 1767, 1615, 1479, 1288, 1251, 1176, 1083, 899 cm^{-1}. MS (EI): *m*/*z* = 184 (M^+). HRMS (EI): calcd. for $C_9H_9FO_3$, 184.0536; found 184.0526.

3-Fluoro-2-methoxyphenyl Acetate (9e): ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.33 (s, 3 H), 3.93 (d, *J* = 1.6 Hz, 3 H), 6.81–6.86 (m, 1 H), 6.97–7.02 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.5, 61.2, 114.6 (d, *J* = 19.8 Hz), 118.3 (d, *J* = 3.3 Hz), 122.8 (d, *J* = 8.2 Hz), 140.2 (d, *J* = 12.3 Hz), 144.2 (d, *J* = 5.0 Hz), 156.0 (d, *J* = 246.8 Hz), 168.8 ppm. IR (neat): $\tilde{\nu}$ = 1769, 1492, 1471, 1281, 1194, 1024, 999, 901, 869 cm^{-1}. MS (EI): *m*/*z* = 184 (M^+). HRMS (EI): calcd. for $C_9H_9FO_3$, 184.0536; found 184.0542.

2-Ethoxy-5-methylphenol (8f) and 2-Ethoxy-4-methylphenol (9f): To a suspension of $NbCl_5$ (175 mg, 0.65 mmol) in dichloroethene (4.4 mL) was added a solution of **7f** (106.0 mg, 0.59 mmol) in dichloroethane (1.5 mL). After stirring for 27 h at room temperature, the reaction mixture was quenched with water (2 mL) and the resulting mixture was extracted with CH_2Cl_2 (5 mL, 3 times). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (hexane/AcOEt, 1:12) to give a 1:1 mixture of **8f** and **9f** (82.8 mg, 93%) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.39–1.44 (m, 6 H), 2.25 (s, 3 H), 2.27 (s, 3 H), 4.03–4.10 (m, 4 H), 5.54 (s, 1 H), 5.65 (s, 1 H), 6.60–6.82 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.9, 20.7, 21.0, 64.3, 64.6, 111.6, 112.5, 114.0, 115.3, 120.2, 121.4, 129.5, 131.0, 143.4, 143.6, 145.5 ppm. IR (neat): $\tilde{\nu}$ = 3536, 2927, 2921, 1509, 1267, 1232, 1197, 1150, 1121, 1040, 794 cm^{-1}. LRMS (EI): *m*/*z* = 152 (M^+). HRMS (EI): calcd. for $C_9H_{12}O_2$, 152.0837; found 152.0842.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all new compounds and NMR study described in Scheme 3.

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