Diethyl ether (10 mL) was added to the reaction mixture. It was washed six times with 8-mL portions of water and each with 10 mL of saturated sodium bicarbonate and 10 mL of brine solution. The organic layer was dried over anhydrous potassium carbonate and filtered, and the solvent was removed under reduced pressure: thin-layer chromatography showed one spot (0.025 g, 1.05×10^{-4} mol, 95%); 80 MHz NMR δ 1.08 (3 H, t), 1.17 (3 H, d), 1.50–2.10 (6 H, m), 3.12 (3 H, s), 4.12–4.40 (2 H, m), 4.50–4.72 (1 H, m).

The mesylate (0.006 g, 2.5×10^{-5} mol) was dissolved in 2 mL of absolute ethanol. 5% Palladium on carbon (1.35 mg) was added to the ethanol solution and it was allowed to stir at room temperature under hydrogen pressure (balloon) for 12 h.

The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. No further purification was necessary (one spot on thin-layer chromatography) (0.0048 g, 2×10^{-5} mol, 80%); 80 MHz NMR δ 1.04 (3 H, t), 1.24 (3 H, d), 1.41–1.98 (6 H, m), 1.98–2.77 (2 H, m), 3.08 (3 H, s), 3.67–4.02 (2 H, m), 4.52–4.79 (1 H, m).

The diol (0.0057 g, 2.4×10^{-5} mol) was dissolved in 1 mL of anhydrous diethyl ether and cooled to 0 °C. Potassium *tert*-butoxide (0.014 g, 1.2×10^{-4} mol) was added in one portion and allowed to stir at 0 °C for 1 h and at room temperature for 2.5 h.

The reaction mixture was diluted with diethyl ether and filtered through a Celite plug. The ether was removed under reduced pressure giving crude epoxy alcohol that was converted to the THF **8** by reaction with trichloroacetic acid in methylene chloride. Gas chromatography of the THF derivatives **7–10** was carried out on a Carbowax 20M capillary column at 75 °C. The elution order of products is **9** (30 min), **10** (36 min), **7** (44 min), and **8** (60 min).

Registry No. **1**, 89122-01-0; **2**, 89122-02-1; **3**, 89122-03-2; **4**, 16015-08-0; **5**, 54774-28-6; **7**, 89122-04-3; **8**, 89194-24-1; **9**, 89194-25-2; **10**, 89194-26-3; **11**, 89122-05-4; **12**, 55968-41-7; **13**, 89122-06-5; **14**, 89194-27-4; **15**, 89194-28-5; **15** mesylate, 89122-08-7; **16**, 89194-29-6; $CH_2{=}CH(CH_2)_2CH(OH)CH_3$, 626-94-8; $MeSO_2Cl$, 124-63-0; $CH_2BrCH_2CH{=}CH_2$, 5162-44-7; CH_3CHO, 75-07-0; CH_3Br, 74-83-9; mercuric pivalate, 32276-77-0; 5-hexen-2-yl methanesulfonate, 89122-07-6; (3*R**,4*R**,7*R**)-4,7-dihydroxyoct-3-yl methanesulfonate, 89122-09-8; *cis*-5-octen-2-ol, 55968-41-7; *cis*-4-hepten-1-ol, 6191-71-5; *cis*-5-octen-2-ol tetrahydropyranyl ether, 63043-82-3; 5,6-epoxyoctan-2-ol tetrahydropyranyl ether, 89122-10-1; *trans*-5-octen-2-ol tetrahydropyranyl ether, 89122-11-2.

Supplementary Material Available: Procedures for synthesis of the alcohol precursors to **2** and **3** and spectral data for THF's **4**, **5**, and **7–10** and dioxanes **13–16** (5 pages). Ordering information is given on any current masthead page.

Synthesis of Phenoxyamines

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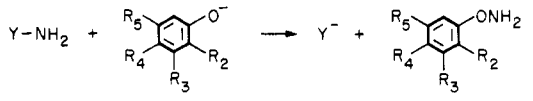
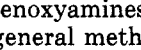
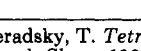
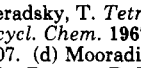
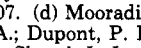
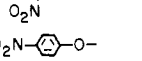
Treatment of phenols with 2,4-dinitrophenoxyamine leads to the synthesis of phenoxyamines through an amine exchange reaction. Yields for this reaction are sensitive to the pK_a of the phenol in a manner explainable in terms of a competing bimolecular decomposition reaction involving the 2,4-dinitrophenoxyamine. By use of an appropriately substituted phenol, this phenomenon can be exploited to give high yields of phenoxyamines having oxygenated substitution patterns that were unattainable by previous methods.

It is well established that *O*-aryl oximes can be converted to benzofurans, presumably through a mechanism paralleling the one postulated for the Fischer indole synthesis.[1,2] These oximes, in turn, can be readily synthesized from phenoxyamines **3**[3] by condensation with a ketone or aldehyde. Thus, phenoxyamines offer the potential for a more convenient, higher yielding, and more general sequence to benzofurans than more conventional methods.[4] Unfortunately, this potential has never been fully realized due to difficulties encountered in the synthesis of the requisite phenoxyamines. In this report we describe an efficient, general method for the synthesis of phenoxyamines.

Scheme I. Synthesis of Phenoxyamines by Amine Exchange



1 **2**$^-$ **3**

Y		R_2	R_3	R_4	R_5
a SO_4^-	a	H	OCH_3	H	OCH_3
b 	b	H	OCH_3	H	H
c Cl^-	c	H	H	H	H
d 	d	H	OTs	H	H
e 	e	H	OMs	H	OMs
f 	f	H	OTs	H	OTs
	g	OMs	H	H	H
	h	OTs	H	H	H
	i		H	H	H
	j	H	H	OTs	H
	k	H	CH_3	Cl	H

The methodologies used in the synthesis of phenoxyamines **3** can be divided into two major categories. In one category, the key step involves an aryl S_N2 substitution of a halobenzene with an oximate anion.[5] This reaction is restricted to halobenzenes having strong ortho or para

(1) (a) Sheradsky, T. *Tetrahedron Lett.* **1966**, 5225. (b) Sheradsky, T. *J. Heterocycl. Chem.* **1967**, *4*, 413. (c) Mooradian, A. *Tetrahedron Lett.* **1967**, 407. (d) Mooradian, A.; Dupont, P. E. *Ibid.* **1967**, 2867. (e) Mooradian, A.; Dupont, P. E. *J. Heterocycl. Chem.* **1967**, *4*, 441. (f) Kaminsky, D.; Shavel, J., Jr.; Meltzer, R. I. *Tetrahedron Lett.* **1967**, 859. (g) Sheradsky, T.; Elgavi, A. *Isr. J. Chem.* **1968**, *6*, 895. (h) Sheradsky, T.; Salemnick, G. *J. Org. Chem.* **1971**, *36*, 1061. (i) Cattanach, C. J.; Rees, R. G. *J. Chem. Soc.* **1971**, 53. (j) Sharkova, L. M.; Aksanova, L. A.; Kucherova, I. F.; Zagorevski, V. A. *Khim. Geterotsikl. Soedin.* **1971**, 762. (k) Bender, D. R.; Hearst, J. E.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2176. (l) Moron, J.; Nguyen, C. H.; Bisagni, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 225.

(2) Robinson, B. *Chem. Rev.* **1969**, *69*, 227.

(3) These compounds are also known as *O*-arylhydroxylamines.

(4) For reviews, see: (a) Cagniant, P.; Cagniant, D. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R.; Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol. 18, p 338. (b) Mustafa, A. "Benzofurans"; Wiley-Interscience, New York, 1974.

(5) For examples, see: Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

0022-3263/84/1949-1348$01.50/0

electron-withdrawing groups, limiting the synthesis to phenoxyamines having such substituents. A more promising and general route to phenoxyamines involves an amine exchange reaction as is presented in Scheme I. Here, reaction proceeds by attack of phenoxide, the amine acceptor, on the amine donor, Y–NH_2. The important characteristic of Y is to render the nitrogen electrophilic by providing a good anionic leaving group. For such amine acceptors, only *O*-(mesitylenesulfonyl)hydroxylamine (**1b**) has given a reasonable yield (54%) of *O*-phenylhydroxylamine (**3c**), the parent compound in this series. However, the utility of this unstable amine donor has been demonstrated for only a limited number of phenoxyamines beyond the parent compound.[6] Among other amine donors, hydroxylamine *O*-sulfonic acid (**1a**) is reported[7] to give a 15% yield of **3c** while chloroamine (**1c**) gives only C-amination.[8] We now describe our results using (2,4-dinitrophenoxy)amine (**1d**, DNPHA) as the amine donor.

Results and Discussion

Because it is readily synthesized,[1b,9] exhibits long-term stability, and has already been used successfully in amine exchange reactions with acceptors other than phenoxides,[10] DNPHA was examined as the amine donor for the synthesis of phenoxyamines. In amination of 7-hydroxy-4,8-dimethylcoumarin with this donor, a 69% yield of the corresponding phenoxyamine was obtained.[1k] Initial results with phenol (**2c**), however, were discouraging. Under identical reaction conditions only a 42% yield of phenoxyamine (**3c**), isolated as its HCl salt, was realized. In addition, isolation of an 80% yield of 2,4-dinitrophenol, an obligatory coproduct of amine exchange, showed that production of the phenol had far outstripped that of **3c**. Initially, we thought that this discrepancy might be accounted for by C-amination to give *o*- or *p*-aminophenol which eluded isolation. However, HPLC analysis of the reaction mixture for *o*- or *p*-aminophenol showed they were absent (<0.03% yield).

With C-amination eliminated as a possibility, we next considered the different behavior between the coumarin and phenol as arising from their different pK_as. Pursuing this hypothesis, we undertook to qualitatively determine the relationship of yield to the pK_a of the amine acceptor. If lowering the pK_a of the amine acceptor increases the yield in the amine exchange reaction, then 4-chloro-3-methylphenol (**2k**) should fare better than phenol by virtue of its electron-withdrawing chloro substituent. In seeking to optimize reaction conditions with this new amine acceptor, we used ^{1}H NMR to directly determine reaction yields. This avoided the complicating factor of isolation losses and allowed for straightforward comparisons through a wide range of reaction conditions.

Parameters that were varied were stoichiometry, solvent, mode and rate of addition, temperature, and base. The course of the reaction was followed through the production of 2,4-dinitrophenoxide by monitoring the absorption at 400 nm where only this species absorbs. After quenching the reaction with trifluoroacetic acid (TFA) and adding a known amount of 2-methoxynaphthalene as a standard, yields were determined by using the ^{1}H NMR signals of the methyl protons of **2k** and **3k**. The yields were based on the integrated weights of the methyl peaks, which gave only a small random error (±5%). This analytical procedure also allowed independent determination of the amount of unreacted **2k** and thus a material balance, which served as an internal check. Optimum conditions were the addition of 200 mol % of **2k** to a NaH suspension in dimethylformamide (DMF) followed by a 2-h addition of 100 mol % of DNPHA. ^{1}H NMR analysis showed a 62% reaction yield and an 87% material balance. Considering the error in the analysis (±5%), this fully accounted for the 4-chloro-2-methylphenol (**2k**).

Table I. Yields in Amine Exchange Using 1d-f as Amine Donors

phenol/amine donor	yields, %		phenoxyamine plus recovered phenol, %
	^{1}H NMR	isolated	
2a/1d	13	a	
2b/1d	34	a	
2c/1d		53[b]	
2d/1d	88	83	93
2e/1d	100	69[c]	
2f/1d	73	72	95
2g/1d	72	45[c]	
2h/1d	88	84	96
2i/1d	69	65	
2j/1d	72	72	93
2k/1d	70	63[b]	
2k/1e	64[d]		
2k/1f	42[d]		

[a] Isolated yields highly variable due to instability to column chromatography. [b] Isolated as the HCl salt. [c] Low isolated yield due to water solubility of the phenoxyamine. [d] These reactions were conducted at 50 °C; all the other reactions were at 20 °C.

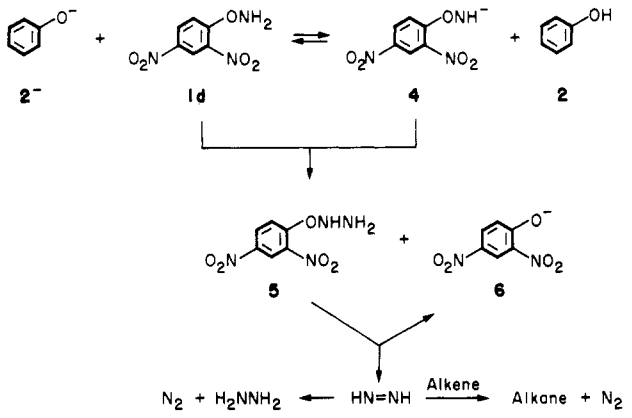
Based on these amination results, we concluded that the amine acceptor must have a mildly electron-withdrawing substituent if DNPHA is to be an effective amine donor. This concept now needed to be applied to the oxygenated phenoxyamines, which would ultimately be required as educts for the benzofurans related to natural products. A suitable modification was necessary to transform the oxygen substituent into an electron-withdrawing group and also to allow its facile reconversion to hydroxy or methoxy. Such a modification has been achieved by use of the sulfonate esters which provide a mildly electron-withdrawing group and lead to successful amination.

For the synthesis of a representative series of oxygenated phenoxyamines, we chose as amine acceptors the readily prepared[11] 2-, 3-, 4-tosyloxy- and 3,5-bis(tosyloxy)phenols, **2h,d,j,f**, to give phenoxyamines with the catechol, resorcinol, hydroquinone, and phloroglucinol substitution patterns, respectively. The results, summarized in Table I, show that these phenols can be aminated in high isolated yields. For the determination of yields directly by ^{1}H NMR, a modification of the previously described analytical procedure was used, omitting the internal standard, 2-methoxynaphthalene, in order to facilitate product isolation. Also, acetonitrile-d_3 was substituted for $CDCl_3$ to maintain solubility of the reaction components.

Thus far, it has been a casual observation that lowering the pK_a of the amine acceptor increases the yield of phenoxyamine. To study this effect in more detail, we also subjected 3,5-dimethoxyphenol (**2a**),[12] 3-methoxyphenol

(6) Endo, Y.; Shudo, K.; Okamoto, T. *Synth. Commun.* **1980**, 461.
(7) Bumgardner, C. L.; Lilly, R. L. *Chem. Ind.* **(London) 1962**, 559.
(8) (a) Theilacker, W. *Angew. Chem.* **1960**, *72*, 498. (b) Theilacker, W.; Ebke, K.; Seidl, L.; Schwerin, S. *Ibid.* **1963**, *75*, 208. (c) Paquette, L. A. *J. Am. Chem. Soc.* **1963**, *85*, 3288.
(9) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239 and references therein.
(10) For examples, see: (a) Sheradsky, T. *Tetrahedron Lett.* **1968**, 1909. (b) Radhakrishna, A. S.; Loudon, G. M.; Miller, M. J. *J. Org. Chem.* **1979**, *44*, 4836.
(11) (a) Maremae, V. M.; Palm, V. A. *Reacts. Sposobn. Org. Soedin.* **1971**, *8*, 591. (b) Kampouris, E. M. *J. Chem. Soc.* **1968**, 2125.

Scheme II. Proposed Side Reaction in the Synthesis of Phenoxyamines



(**2b**), and 3,5-bis[(methylsulfonyl)oxy]phenol (**2e**)[13] to amine exchange. When the yields of 13%, 34%, and 100%, respectively, for these amine acceptors are combined with the 53% yield from phenol (**2c**) and 88% yield from 3-(tosyloxy)phenol (**2d**), then the relationship between yield and pK_a becomes evident. All these yields are based on ^{1}H NMR analysis, with the exception of phenol (**2c**), and are calculated by using the ratio of peak areas for unreacted amine acceptor to phenoxyamine product. Therefore, these ^{1}H NMR results represent maximum obtainable yields. A direct comparison for all these amine acceptors based on isolated yields was not possible due to the instabilities of **2a** and **2b**.

To determine if the above-mentioned substituent effect could be further exploited, the nature of the sulfonyloxy group was varied. With 2-[[(*p*-fluorophenyl)sulfonyl]-oxy]phenol (**2i**) the more electron-withdrawing substituent on phenol as compared to **2d** might result in a higher yield. Unfortunately, just the opposite occurred; a 65% yield was obtained. As with **2f**, which should have been comparable to **2e** as an amine acceptor, this phenol deviates from the trend. However, with 2-(mesyloxy)phenol (**2g**), the weaker electron-withdrawing substituent did give the expected lower yield (76%). To obtain the phenols **2g** and **2i**, the corresponding bis derivatized catechols were hydrolyzed by using 200 mol % KOH in MeOH in a procedure adapted from the reported synthesis of **2f**[11b] to give the monosubstituted compound in moderate yields (~55%).

Although the relationship of pK_a to yield is not straightforward, it is explainable in terms of competitive rates between amine exchange and a side reaction involving bimolecular decomposition of the amine donor. In the amination of ester enolates with DNPHA, yields are reported[10b] to increase as the pK_a of the ester decreases and the amount of 2,4-dinitrophenol isolated was always higher than would be expected on the basis of these yields. These results closely parallel ours with phenols as the amine acceptor. As an explanation, the acceptor was postulated also to act as a base and to deprotonate the amine donor. The resulting species, DNPHA$^-$ (**4**), then would react with another molecule of **1d** to give 2,4-dinitrophenoxide (**6**) and (2,4-dinitrophenoxy)hydrazine (**5**), which decomposes rapidly to **6** and diimide (Scheme II). To demonstrate whether such a decomposition was occurring under the conditions used in our amine exchange reaction, we stirred a 0.5 M DNPHA solution in DMF at room temperature in the presence of norbornylene and found **6** produced concommitant with reduction to give norbornane. Consideration of these results leads to the conclusion that aminating agent is being lost through bimolecular decomposition.

To slow the decomposition of DNPHA (**1d**), we need to lower the equilibrium concentration of DNPHA$^-$ (**4**). This would be accomplished by using an amine acceptor that was a weaker base; however, this now would also be a poorer nucleophile, so the rate of amine exchange would be reduced as well. Because the former effect is found to be dominant, the rate of amine exchange increases relative to DNPHA decomposition as the pK_a of the phenol is decreased. If the pK_a is lowered below a certain point, however, the amine exchange reaction becomes so sluggish that the concentration of **1d** builds up. Because the destruction of **1d** has a second-order dependence on this concentration, the rate of decomposition increases relative to amine exchange, and thus the yields begin to drop. Phenols **2f** and **2i** provide examples where the pK_a has been lowered too much. However, with **2e** the optimum pK_a has been attained, resulting in a quantitative yield.

With the above explanations in mind we attempted to favorably affect the rate of amine exchange relative to decomposition by varying the structure of the amine donor. Therefore, we examined the behavior of 3,4-dinitrophenoxy- and (*p*-nitrophenoxy)amines (**1e** and **1f**) in amine exchange reactions. With these amine donors the acidity of the amino hydrogens is being lowered in order to reduce the rate of bimolecular decomposition. However, with **2k**$^-$ as the amine acceptor, no significant improvement in yield was found for **1e** (64%) as compared to **1d** (60%). Far worse was **1f**, which gave a poorer yield (42%) of **3k**. All these aminations were conducted under identical reaction conditions and at slightly more elevated temperatures (50 °C) than normally employed (20 °C) in order to obtain a reasonable rate of reaction with **1f**. The syntheses of **1e** and **1f** were derived from the literature[14a] and involved an aryl S_N2 substitution on the appropriately substituted chlorobenzene by the anion of ethyl *N*-hydroxyacetimidate.

The failure to increase amination yields by variations in the amine donor again can be explained in terms of competitive rates. Although **1e** and **1f** have less acidic N hydrogens than does **1d**, they also have poorer leaving groups on nitrogen, making this center less electrophilic. This latter effect would decrease the rate of amine exchange and thus effectively offset the decrease in the rate of decomposition, keeping the relative rate the same as seen with **1e**. With **1f**, however, the rate of amine exchange has been made so slow that the concentration of amine donor builds up. So again, decomposition increases relative to amine exchange, and the opposing effects no longer cancel, causing the yield to drop.

Conclusion

We have reported an effective method to synthesize a previously unavailable class of oxygenated phenoxyamines by employing an amine exchange reaction with DNPHA as the amine donor and readily synthesized phenols as the amine acceptors. This method does require an excess of the acceptor; however, since amine exchange proceeds nearly quantitatively and there are no significant side reactions, recovery of unreacted starting material is straightforward. In addition, we have shown that the amine exchange reaction is sensitive to the pK_a of the phenol. As a practical application of this phenomenon, one can synthesize oxygenated phenoxyamines in high

(12) Nakazawa, K.; Matsuura, S. *J. Pharm. Soc. Jpn.* **1953**, *73*, 751.
(13) Helferich, B.; Papalambrou, P. *Liebigs Ann. Chem.* **1942**, *551*, 235.
(14) (a) Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 3833. (b) Blakeley, R. L.; Zerner, B. *Chem. Ind.* (**London**) **1973**, 133.

Table II. Physical Constants and Spectral Data for Phenols 2 and Phenoxyamines 3

compd	mp °C (recrystn solvent)	^{1}H NMR ($CHCl_3$, J in Hz)	elemental analyses or HRMS: calcd C, H, N or calcd M$^+$	elemental analyses or HRMS: found C, H, N or found M$^+$
3a	oil[a]	3.77 (s, 6 H), 5.82 (br s, 2 H), 6.09 (t, 1 H, J = 2), 6.35 (d, 2 H, J = 2)	169.0739	169.0743
3b	oil[a]	3.69 (s, 3 H), 5.75 (br s, 2 H), 6.40 (ddd, 1 H, J = 1, 2, 8), 6.61 (ddd, 1 H, J = 1, 2, 8), 6.66 (t, 1 H, J = 2), 7.07 (t, 1 H, J = 8)	139.0634	139.0637
3d	69-70 (EtOH/hex)	2.44 (s, 3 H), 5 84 (br s, 2 H), 6.51 (ddd, 1 H, J = 1, 2, 8), 6.91 (t, 1 H, J = 2), 6.98 (dd, 1 H, J = 1, 2, 8), 7.13 (t, 1 H, J = 8), 7.31 (d, 2 H, J = 9), 7.73 (d, 2 H, J = 9)	55.9, 4.7, 5.0	55.8, 4.7, 5.0
3e	98-100 (EtOH/hex)	3.19 (s, 6 H), 6.25 (s, 2 H), 6.82 (t, 1 H, J = 2, 7.11 (d, 2 H, J = 2)	32.3, 3.7, 4.7	32.5, 3.8, 4.5
3f	oil[b]	2.43 (s, 6 H), 5.85 (br s, 2 H), 6.23 (t, 1 H, J = 2), 6.73 (d, 2 H, J = 2), 7.30 (d, 4 H, J = 8), 7.68 (d, 4 H, J = 8)	53.4, 4.3, 3.1	53.3, 4.0, 2.8
2g	44-46 ($bp_{1.6}$ = 155)	3.24 (s, 3 H), 6.94 (dt, 1 H, J = 2, 8), 7.06 (dd, 1 H, J = 2, 8), 7.22 (dt, 1 H, J = 2, 8), 7.26 (dd, 1 H, J = 2, 8)	44.7, 4.3	44.6, 4.3
3g	41-42[c]	3.17 (s, 3 H), 6.05 (br s, 2 H), 6.97 (ddd, 1 H, J = 2, 7, 7), 7.26 (ddd, 1 H, J = 2, 7, 7), 7.61 (dd, 1 H, J = 2, 7)	41.4, 4.5, 6.9	41.4, 4.5, 6.8
3h	71-72 (EtOH/hex)	2.44 (s, 3 H), 5.71 (br s, 2 H), 6.85 (ddd, 1 H, J = 2, 8, 8), 7.29 (d, 2 H, J = 8), 7.44 (ddd, 1 H, J = 2, 8, 8), 7.75 (d, 2 H, J = 8)	55.9, 4.7, 5.0	56.1, 4.8, 5.0
2i	84-86 ($MeOH/H_2O$)	5.50 (br s, 1 H), 6.78 (dt, 1 H, J = 2, 8), 6.84 (dd, 1 H, J = 2, 8), 6.97 (dd, 1 H, J = 2, 8), 7.21 (t, 2 H, J = 9), 7.90 (dd, 2 H, J = 5, 9)	53.7, 3.4	53.8, 3.3
3i	83-84 ($EtOH/H_2O$)	5.73 (s, 2 H), 6.88 (ddd, 1 H, J = 2, 8, 8), 7.02 (dd, 1 H, J = 2, 8), 7.22 (ddd, 1 H, J = 2, 8, 8), 7.24 (t, 2 H, J = 9), 7.47 (dd, 1 H, J = 2, 8), 7.90 (dd, 2 H, J = 5, 9)	50.9, 3.6, 4.9	50.5, 3.7, 4.7
3j	70.5-71.5 (EtOH/hex)	2.44 (s, 3 H), 5.86 (s, 2 H), 6.85 (d, 2 H, J = 9), 7.02 (d, 2 H, J = 9), 7.30 (d, 2 H, J = 8), 7.68 (d, 2 H, J = 8)	55.9, 4.7, 5.0	56.2, 4.8, 5.0
3k	oil[a]	2.34 (s, 3 H), 5.84 (br s, 2 H), 6.91 (dd, 1 H, J = 3, 9), 7.01 (d, 1 H, J = 3), 7.21 (d, 1 H, J = 9)	157.0295	157.0291

[a] Purified on a Chromatotron (99/1, $CHCl_3$/MeOH). [b] Purified by column chromatography (50/33/17 hexane/$CHCl_3$/EtOAc). [c] Purified by column chromatography (43/34/23 EtOAc/hexane/$CHCl_3$).

yield through variations in the oxygen substituent.

Experimental Section

General Methods. All melting points were taken in open capillaries on a Buchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Varian EM-390 (90 MHz) CW-spectrometer or the Berkeley 250 MHz FT-spectrometer. Chemical shifts are expressed in ppm downfield from internal Me_4Si. ^{19}F NMR were recorded on a Varian EM-390 spectrometer and UV data obtained on a Varian 219 spectrophotometer. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley. High-resolution mass spectra were obtained on a Kratos MS-50 instrument. Gas chromatographic analysis for norbornane[15] was done on a Varian Aerograph Series 1400 gas chromatograph using a 4 mm × 1.5 m 3% OV-1 AW-DMCS glass column. High-pressure liquid chromatography (HPLC) was done on an Altex system consisting of two Model 110A pumps, a Model 115-10 UV-VIS detector, and a Model 420 microprocessor. Preparative low-pressure chromatography was done on 70–230 mesh SiO_2 (E. Merck). Thin-layer chromatography (TLC) was done on precoated silica G-60 F-254 aluminum-backed plates (E. Merck). Preparative TLC was done with a Model 7924 Chromatotron using a 1-mm layer of silica gel PF-254. Dimethylformamide (DMF) was dried over CaH_2 before being distilled under reduced pressure.[16] Pyridine was dried over BaO than CaH_2 before distilling. 3-Methoxyphenol (**2b**) and *p*-fluorobenzenesulfonyl chloride were purified by distillation under reduced pressure. Phenol (**2c**) was dried by distillation from a benzene solution. All distillations were performed under N_2. 4-Chloro-3-methylphenol (**2k**) was purified by recrystallization from ligroin (30–60 °C). 2-Methoxynaphthalene and 1-chloro-3,4-dinitrobenzene were recrystallized from Et_2O. Catechol was recrystallized from toluene. *p*-Nitrochlorobenzene was purified by recrystallizing from 95% EtOH followed by drying over P_2O_5. 2,4-Dinitrophenoxyamine (**1d**) was synthesized as reported.[9] All reactions were conducted under N_2.

2-[(Methylsulfonyl)oxy]phenol (2g). To 10 g of catechol (91 mmol) mechanically stirred in pyridine (60 mL) at 0 °C was added a solution of 16 mL of methanesulfonyl chloride (0.207 mol) in 40 mL of cold pyridine over 0.5 h. After an additional 8 h of stirring at 0 °C, the pyridine was evaporated, water (100 mL) was added, and the evaporation repeated. The residue was filtered, washed with water, and dried over P_2O_5 to yield 23.5 g, 97%, of 1,2-bis[(methylsulfonyl)oxy]benzene: mp 101–103 °C; ^{1}H NMR (acetonitrile-d_3) δ 3.30 (s, 6 H); 7.3–7.6 (m, 4 H).

To 1.33 g of 1,2-bis[(methylsulfonyl)oxy]benzene (5 mmol) stirred in 10 mL of MeOH was added 2.8 mL of 20% methanolic

(15) Norbornane was obtained through hydrogenation of norbornylene using PtO_2 and H_2 at 50 psi in EtOAc.

(16) Care must be taken not to overheat the DMF during distillation, otherwise any dimethylamine that is produced will react with DNPHA to give a blood-red solution in contrast to the normal light yellow solution.

KOH. The reaction was monitored by RP-HPLC using an Altex Ultrasphere ODS column (4.6 × 250 mm), eluting with 50% MeCN at 1.0 mL/min: t_R 1,2-bis[(methylsulfonyl)oxy]benzene, 3.1 min; **2g**, 2.5 min. After 90 min at room temperature the reaction mixture was poured into 40 mL of cold water and washed with Et_2O (2 × 20 mL). The aqueous layer was acidified to pH 6 with dilute H_2SO_4 and extracted with Et_2O (3 × 40 mL), and the ether phase was washed with brine, dried ($MgSO_4$), and evaporated to an oil, which was distilled (Kugelrohr) to give 632 mg, 67%, of **2g**. For characterization data see Table II.

2-[[(*p*-Fluorophenyl)sulfonyl]oxy]phenol (2i). The procedure for the synthesis of 1,2-bis[[(*p*-fluorophenyl)sulfonyl]-oxy]benzene was identical with that above except that *p*-fluorobenzenesulfonyl chloride was used in place of methanesulfonyl chloride. From 2.5 g (23 mmol) of catechol was obtained 8.94 g, 92%, of the crude bis derivative: mp 149–153 °C; ^1H NMR ($CDCl_3$) δ 5.92 (t, 1 H, J = 8 Hz), 6.28 (dd, 1 H, J = 2, 8 Hz), 6.67 (dd, 1 H, J = 2, 8 Hz), 6.73 (dd, 1 H, J = 2.8 Hz), 7.34 (t, 2 H, J = 9 Hz), 8.10 (d, 1 H, J = 9 Hz), 8.13 (d, 1 H, J = 9 Hz), 8.31 (s, 4 H). Mono hydrolysis was conducted as above to give **2i** in 44% yield. For characterization data see Table II.

(*p*-Nitrophenoxy)amine (1f). To 2.80 g of sublimed *t*-BuOK (25 mmol) in DMF (25 mL) cooled to 0 °C was added 3.55 g (34 mmol) of *N*-hydroxyacetimidate[17] in DMF (10 mL) over a 5-min period. After 30 min of stirring, 3.15 g (20 mmol) of *p*-nitrochlorobenzene in 35 mL of DMF was added over a 4-h period, and the reaction was then allowed to reach room temperature and stirred for an additional 16 h. The DMF was evaporated, giving a residue which was partitioned between Et_2O (50 mL) and 0.5 N NaOH (50 mL), and the ethereal layer was washed with brine, dried ($MgSO_4$), and evaporated to give 2.92 g, 65% yield, of ethyl *N*-(*p*-nitrophenoxy)acetimidate: mp 103–105 °C; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H, J = 7 Hz), 2.10 (s, 3 H), 4.18 (q, 2 H, J = 7 Hz), 7.18 (d, 2 H, J = 9 Hz), 8.17 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.5; H, 5.5; N, 12.4.

To 2 mL of cold 70% $HClO_4$ was added 500 mg (2.23 mmol) of ethyl *N*-(*p*-nitrophenoxy)acetimidate, and the suspension was stirred for 2 h in the cold and then allowed to reach room temperature. After being stirred an additional 2 h, the reaction mixture was poured onto 20 mL of cold water, the pH was adjusted to 7 with aqueous NaOH, and the precipitate that formed was collected by filtration and washed thoroughly with 0.5 M NaOH and then water. Drying over P_2O_5 left 241 mg, 70% yield, of **1f**: mp 124–125 °C dec from EtOAc/ligroin [lit. mp[14b] 126–127 °C dec]; ^1H NMR ($CDCl_3$) δ 6.88 (br s, 2 H), 7.05 (d, 2 H, J = 9 Hz), 7.97 (d, 2 H, J = 9 Hz).

(3,4-Dinitrophenoxy)amine (1e). The precursor of **1e**, ethyl *N*-(3,4-dinitrophenoxy)acetimidate was synthesized according to the procedure above except that 1-chloro-3,4-dinitrobenzene was used in place of *p*-nitrochlorobenzene. On a 20-mmol scale 5.46 g of the crude imidate was obtained as a mixture of *E* and *Z* isomers: ^1H NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 9 Hz), 2.11 and 2.33 (s, total 3 H), 4.18 (q, 2 H, J = 9 Hz), 6.72 (dd, 1 H, J = 3, 9 Hz), 7.42 (d, 1 H, J = 3 Hz), 8.00 (d, 1 H, J = 9 Hz).

To 50 mL of cold 70% $HClO_4$ was added 1.0 g (3.89 mmol) of the imidate in portions. After being stirred for 2 h at 0 °C, the reaction was allowed to reach room temperature and stirred an additional 16 h, then it was poured into 50 mL cold water and adjusted to pH 7 with aqueous NaOH. The resulting precipitate was collected, washed thoroughly with cold water, and dried over P_2O_5, giving 604 mg, 78% yield, of **1e**: mp 143–145 °C from EtOH/hexane; ^1H NMR (acetonitrile-d_3) δ 6.40, 6.48 (s, 2 H), 6.65 (dd, 1 H, J = 3, 9 Hz), 7.58 (d, 1 H, J = 3 Hz), 7.88 (d, 1 H, J = 9 Hz). Anal. Calcd for $C_6H_5N_3O_5$: C, 36.2; H, 2.5; N, 21.1. Found: C, 36.1; H, 3.2, N, 20.9.

General Procedures for the Synthesis of Phenoxyamines. Sodium hydride (110 mg, 43% oil dispersion) was washed with hexane (2 × 2 mL), and after the final wash, the vessel was swept through with N_2 and 6.5 mL of DMF was added. To the magnetically stirred suspension at 0 °C was added dropwise over a 5-min period a 5.5 mL DMF solution of the phenol (**2**, 3.0 mmol). After the addition, the reaction mixture was allowed to reach room temperature (20 °C, 30 min), whereupon a 3.5 mL DMF solution containing 300 mg of **1d** was added by syringe pump over 2 h. The reaction mixture was stirred an additional 2 h and then quenched with 115 μL (1.5 mmol) of TFA, poured into a cold 20% saturated $NaHCO_3$ solution, and extracted with Et_2O (1 × 80 mL, 3 × 40 mL). The combined organic layers were extracted with 0.5 N NaOH (1 × 80 mL, 3 × 40 mL), washed with brine, dried ($MgSO_4$), and evaporated. Isolation of the individual phenoxyamines **3** from the residues proceeded as follows. **3a** and **3b**: the residues were purified on a chromatotron: TLC (99/1, $CHCl_3$/MeOH) R_f (**3a**) 0.31; R_f (**3b**) 0.37. For further characterization data, see Table II. **3c**: the residue was dissolved into 5 mL of anhydrous Et_2O, the chilled solution was saturated with HCl(g), and the resulting precipitate was collected and washed with anhydrous Et_2O to give **3c**·HCl: mp 114 °C dec from CH_2Cl_2/EtOH [lit. mp[18] 136 °C dec]. Anal. Calcd for C_6H_8NOCl: C, 49.5; H, 5.5; N, 9.6. Found: C, 49.6; H, 5.6; N, 9.6. **3d**, **3e**, **3h**, **3i**, **3j**: the residues were solids that were recrystallized by using the solvent systems given in Table II. **3f** and **3g**: the residues were oils that were purified by column chromatography: TLC R_f (**3f**) 0.24 (50/30/17, hexane/$CHCl_3$/EtOAc), R_f **3g** 0.28 (43/34/23, EtOAc/hexane/$CHCl_3$). **3k**: the residue was a liquid that was dissolved in 10 mL of anhydrous Et_2O, the chilled solution was saturated with HCl(g), and the resulting precipitate was collected to give **3k**·HCl as a very hygroscopic solid. The free base was regenerated by adding the solid to cold 0.5 N NaOH and extracting with Et_2O, from which the residue was further purified on a chromatotron: TLC (99/1, $CHCl_3$/MeOH) R_f (**3k**) 0.49. For further characterization data on all compounds, see Table II.

For the recovery of unreacted phenol in each case the alkaline extract was chilled, acidified to pH 6 with dilute H_2SO_4, and extracted with Et_2O (1 × 80 mL, 2 × 40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Recovered **2d**, **2f**, **2h**, and **2j** were further purified by column chromatography using 47/31/22 hexane/$CHCl_3$/EtOAc.

There were some minor variations in the general reaction conditions. In the synthesis of **3k** using **1e** and **1f** as the amine donors, addition of the aminating agent was to a solution of the amine acceptor at 50 °C. In the synthesis of **3e** and **3f**, the reaction mixture after quenching was poured into a chilled NaCl solution (20% saturation); isolation then proceeded by the general process.

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Registry No. **1d**, 17508-17-7; **1e**, 89232-54-2; **1f**, 33543-55-4; **2a**, 500-99-2; **2b**, 150-19-6; **2c**, 108-95-2; **2d**, 18622-12-3; **2e**, 89232-55-3; **2f**, 20032-62-6; **2g**, 59722-34-8; **2h**, 35616-01-4; **2i**, 89232-56-4; **2j**, 35616-03-6; **2k**, 59-50-7; **3a**, 89232-57-5; **3b**, 89232-58-6; **3c**, 4846-21-3; **3c**·HCl, 6092-80-4; **3d**, 89232-59-7; **3e**, 89232-60-0; **3f**, 89232-61-1; **3g**, 89232-62-2; **3h**, 89232-63-3; **3i**, 89232-64-4; **3j**, 89232-65-5; **3k**, 89232-66-6; **3k**·HCl, 89232-67-7; catechol, 120-80-9; 1,2-bis[(methylsulfonyl)oxy]benzene, 64931-04-0; *p*-fluorobenzenesulfonyl chloride, 349-88-2; *p*-nitrochlorobenzene, 100-00-5; ethyl *N*-(*p*-nitrophenoxy)acetimidate, 83077-00-3; (*E*)-ethyl *N*-(3,4-dinitrophenoxy)acetimidate, 89232-68-8; (*Z*)-ethyl *N*-(3,4-dinitrophenoxy)acetimidate, 89232-69-9.

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