New Synthesis of Substituted Benzylamines. Novel Application of the Mitsunobu Reaction To Convert Substituted Benzyl Alcohols to Amines†

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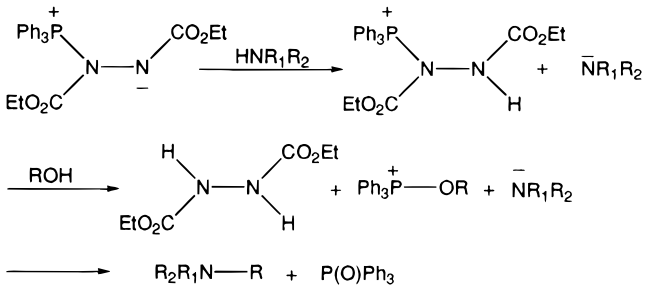
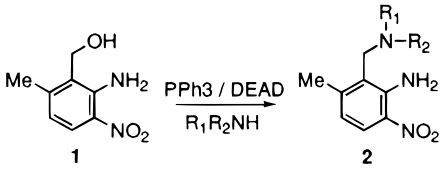
Introduction

Synthesis of amines from alcohols using the Mitsunobu reaction is well-documented.[1] In most cases, for the success of the reaction it is important to have protected amines as the acidic component (p$K_a \sim 8$) of the reaction in the form of amides,[2] phthalimides,[3] *N*-alkylsulfonamides,[4] *N*-methyltrifluoromethanesulfonamides,[5] or hydrazoic acid[6] which undergo deprotonation to generate the reactive nucleophile. The yields are higher with lower pK_a of the amine component. The mechanism of this conversion has been the topic of investigation for several years and the one that best explains this transformation involves the initial formation of a quaternary phosphonium salt by addition of PPh_3 to diethylazodicarboxylate (DEAD) followed by protonation of the salt by the substituted amine moiety (Scheme 1).[1] The resulting complex reacts with the alcohol to give the alkoxyphosphonium salt, which undergoes an S_N1 or S_N2 type displacement to give the desired amines. Thus, this process essentially precludes the use of various basic secondary amines as the amine component to synthesize tertiary amines. There are very few examples in the literature where the Mitsunobu reaction has been used to form substituted amines, especially benzylic amines, by reacting alcohols with secondary amines with pK_a higher than 8. In two reports[7,8] an intramolecular Mitsunobu reaction between benzylic amino alcohols yielded cyclic amines with defined amine substituents, which considerably narrowed the scope of the reaction. Recently,[9] Mitsunobu-mediated intramolecular cyclization of benzyl amines has been carried out using a variety of azodicarboxamides. However, from this study it is evident that there are several limitations for the success of this reaction. In one of our ongoing projects, we have a need for a variety of secondary and tertiary benzylamines with 2-amino-3-nitro substitutions on the benzene ring. In this context we successfully used the

Scheme 1



Scheme 2. Synthesis of Benzylamines 2 using Benzyl Alcohols 1 under Mitsunobu Reaction Conditions



Mitsunobu reaction conditions for the synthesis of these substituted benzylamines **2** by reacting an activated benzyl alcohol **1**[10] with primary or secondary amines (Scheme 2). These benzylamines **2** are also versatile intermediates for the synthesis of a variety of biologically active nitrogen heterocycles.[11]

Results and Discussion

The benzylamines synthesized by the present method are shown in Table 1. In a typical reaction a solution of 6-methyl-3-nitro-2-aminobenzyl alcohol (**1**) (1 equiv), PPh_3 (1.5 equiv), and an appropriate amine (1.5 equiv) was treated with DEAD (1.5 equiv) at 5 °C. The reaction mixture was allowed to warm to room temperature and, after purification by chromatography, gave the corresponding benzylamines **2** in fair to good yields. In general, the yields suffered when the amines were less basic (pK_a < 9; amines listed in the table are in the range of 10−12) or were sterically hindered. For example, the reaction with morpholine (p$K_a \sim 8$, Table 1, no. 18) or diisopropylamine (Table 1, no. 5) did not give the desired product and mainly unreacted starting material was recovered. These derivatives were made by reacting these amines with the more reactive benzyl bromide **3**, which is generated by treating benzyl alcohol **1** with CBr_4/PPh_3 in ether (Scheme 3). Efforts to improve the yields by altering the sequence of addition of reagents were not successful. For example, addition of the amine and alcohol to the mixture of PPh_3/DEAD complex or the addition of the amine to a mixture of the alcohol **1** and PPh_3/DEAD complex did not improve the results obtained using the procedure described earlier. Addition of the amine to the mixture of alcohol **1** and PPh_3/DEAD complex gave mainly the hydrazine derivative **4**. Hence, it is important to have the desired nucleophilic amine in

† Dedicated to Dr. S. Ramanathan (Sandoz Research Labs, India), on his 60th birthday.

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Table 1. Benzylamines 2 Synthesized via the Mitsunobu Protocol

entry no.	R_1	R_2	yield (%)
1	Me	Me	86
2	Et	Et	45
3	*n*-Pr	*n*-Pr	56
4	*n*-Bu	*n*-Bu	51
5	*i*-Pr	*i*-Pr	(82)[a]
6	Me	*i*-Pr	43
7	Me	*n*-Bu	64
8	Me	cyclohexyl	60
9	Me	2-CH_2-1,3-dioxolane	63
10	H	cyclohexyl	50
11	azetidinyl		33
12	pyrrolidinyl		80
13	2-methylpyrrolidinyl		62
14	2,5-dimethylpyrrolidinyl		65
15	piperidinyl		84
16	2-methylpiperidinyl		49
17	4-methylpiperidinyl		74
18	3,5-dimethylpiperidinyl		76
19	morpholinyl		(43)[a]
20	thiomorpholinyl		70
21	4-methylpiperazinyl		77
22	azepinyl		79
23	octahydroquinolinyl		81
24	octahydroisoquinolinyl		80

[a] Yield starting from benzyl bromide derivative **3**.

Scheme 3. Synthesis of Benzylamines 2 via Benzyl Bromide 3

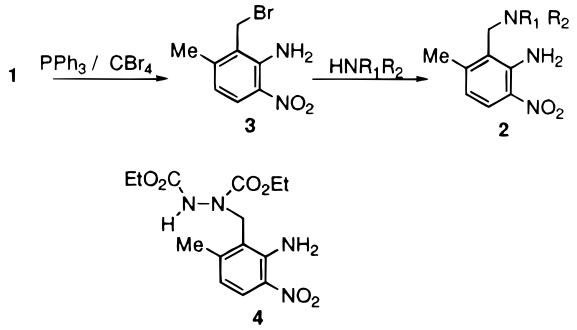
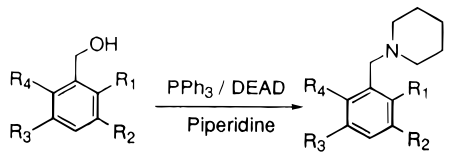


Table 2. Mitsunobu Reaction of Piperidine with Variously Substituted Benzyl Alcohols



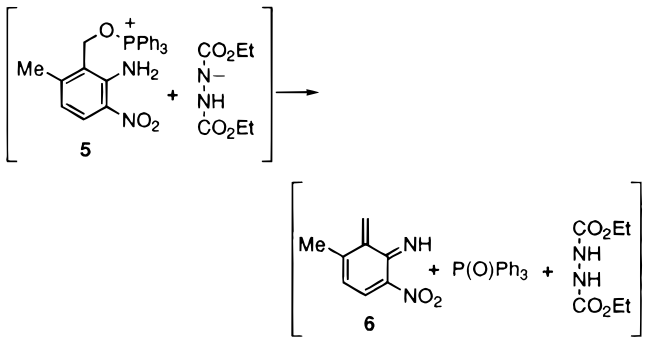
entry no.	R_1	R_2	R_3	R_4	yield (%)
1	H	H	H	H	NR[a]
2	NH_2	H	H	H	NR
3	H	NO_2	H	H	NR
4	NH_2	NO_2	H	H	60
5	NH_2	Br	Br	H	68
6	NMe_2	NO_2	H	Me	NR
7	OH	NO_2	H	H	27

[a] NR = no reaction.

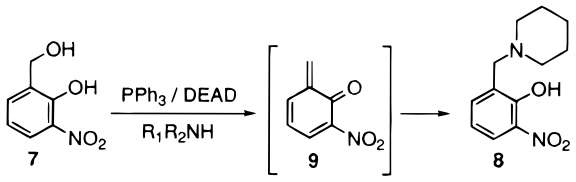
the reaction mixture before the hydrazine base is generated in the reaction.

Several other experiments were carried out to investigate the mechanism of the reaction (Table 2). On the basis of these results it was obvious that a meta electron-withdrawing group and an amino group ortho to the hydroxymethyl moiety are very important for the success of these reactions. Unsubstituted benzyl alcohol, *o*-aminobenzyl alcohol, or *m*-nitrobenzyl alcohol did not

Scheme 4



Scheme 5



give the desired benzylamines on reaction with piperidine as the amine under the Mitsunobu reaction conditions described earlier. These observations can be explained by the mechanism postulated in Scheme 4. Thus, the reaction of benzyl alcohol **1** with amines is probably a typical conjugate addition of the nucleophilic amines to an azaquinodimethane intermediate **6**. The azaquinodimethane intermediate in turn could be generated via the rearrangement of the PPh_3 complex **5** by initial deprotonation of the *o*-amino group. The significance of the electron-withdrawing group ortho to the amine functionality in **1** is thus obvious, in that it facilitates deprotonation of the primary amino group by the hydrazine base to generate the azaquinodimethane intermediate **6**. In support of this assumption is the observation that the 3,5-dibromobenzyl alcohol derivative (entry no. 5, Table 2) also produced the desired amine under identical Mitsunobu conditions in good yield. The reaction of the *N,N*-dimethylamino compound (no. 6) with piperidine under the reaction conditions mentioned above did not give the desired benzylamine. This result confirms the importance of the deprotonation step and the generation of the azaquinodimethane intermediate. As noted in Scheme 5, appropriately substituted phenolic alcohols also underwent this reaction to yield the desired benzylamines. The success of this reaction further supports the mechanism postulated for the formation of the benzylamines, which in this case probably proceeds via the conjugate addition of piperidine to the *o*-quinone methide intermediate **9**. The desmethyl analog (Table 2, no. 4, R_4 = H) gave the desired benzylamine in comparable yield to the corresponding methyl derivative (Table 1, no. 14) indicating that the methyl group does not play a major role in the formation of the products or the overall mechanism of the reaction.

Conclusion

In summary, we have developed a new method for the synthesis of versatile multifunctional benzylamines using mild Mitsunobu conditions which most likely proceeds via conjugate addition of amines to the azaquinodimethane or *o*-quinodimethane intermediates. On the basis of this mechanism we are currently exploring alternate routes

to synthesize other 6-hetero-2-nitroanilines more efficiently.

Experimental Section

Materials. All chemicals were purchased from Aldrich and were used without additional purification. ^{1}H-NMR spectra were recorded at 400 MHz in $CDCl_3$. The starting material for entry no. 7 in Table 2, 2-hydroxy-3-nitrobenzyl alcohol, was made by reducing a solution of 3-nitrosalicyclic acid in THF with BH_3·-THF (1.0 M solution). 2-(*N*,*N*-Dimethylamino)-6-methyl-3-nitrobenzyl alcohol (entry 6, Table 2) was made by treating the O-TIPS ether of **1** with methyl iodide in the presence of NaH in DMF and subsequent deprotection of the silyl ether with TBAF solution in THF.

General Procedure for Synthesis of Substituted Benzylamines Starting from the Corresponding Benzyl Alcohols under Mitsunobu Conditions. To a stirred solution of the benzyl alcohol (0.91 g, 5 mmol), PPh_3 (1.96 g, 7.5 mmol), and amine, e.g. N-methylisopropylamine (0.547 g, 7.5 mmol) in benzene (10 mL) was added DEAD (1.31 g, 7.5 mmol) under N_2 at 5 °C. The reaction mixture was allowed to warm to rt and was stirred for additional 2 h. The reaction was monitored by TLC (SiO_2, petroleum ether/ethyl acetate, 1:1). The dark reaction mixture was concentrated on a rotary evaporator (~50 °C) to give a viscous oil. The product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 95:5 to 80:20). The yield of the product (Table 1, entry no. 6) was 0.55 g, 43%: ^{1}H-NMR δ 1.02 (d, 3H, J = 6.6 Hz), 1.03 (d, 3H, J = 6.6 Hz), 2.07 (s, 3H), 2.28 (s, 3H), 2.81 (m, 1H), 6.41 (d, 1H, J = 9.1 Hz), 7.9 (d, 1H, J = 9.1 Hz), 7.89−7.9 (bs, 2H); MS (CI) m/z = 237.3 (M + H). Anal. Calcd for $C_{12}H_{19}N_3O_2$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.9; H, 8.01; N, 17.8.

Spectral data for the compounds (entry nos) synthesized and listed in Table 1 follow.

No. 1: ^{1}HNMR δ 2.21 (s, 6H), 2.35 (s, 3H), 3.55 (s, 2H), 6.45 (d, J = 6.5 Hz, 1H), 7.77 (bs, 2H), 7.95 (d, J = 6.5 Hz, 1H); MS (CI) m/z 210 (M + H).

No. 2: ^{1}H-NMR δ 1.03 (t, J = 7.2 Hz, 6H), 2.28 (s, 3H), 2.46 (q, 4H), 3.63 (s, 2H), 6.41 (d, J = 8.8H, 1 Hz), 7.90 (d, J = 8.8 H, 1 Hz), 7.95 (bs, 2H); MS (CI) m/z 238 (M + H).

No. 3: ^{1}H-NMR δ 0.83 (t, J = 7.3 Hz, 6H), 1.48 (septet, 4H), 2.27 (s, 3H), 2.32 (t, J = 7.4 Hz, 4H), 3.62 (s, 2H), 6.42 (d, J = 8.8 Hz, 1H) 7.91 (d, J = 8.8 Hz, 1H); MS (CI) m/z 266 (M + H).

No. 4: ^{1}H-NMR δ 0.84 (t, J = 7.3 Hz, 6H), 1.23 (sextet, 4H), 1.43 (quintet, 4H), 2.27 (s, 3H), 2.35 (t, J = 7.4 Hz, 4H), 3.62 (s, 2H), 6.42 (d, J = 9 Hz, 1H), 7.91(d, J = 8.8 Hz, 3H), 7.9−7.92 (bs, 2H); MS (CI) m/z 294 (M + H).

No. 5: ^{1}H-NMR δ 1.10 (d, J = 6.6 Hz, 12H), 2.34 (s, 3H), 3.03 (septet, 2H), 3.82 (s, 2H), 6.43 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 8.15 (bs, 2H); MS (CI) m/z 266 (M + H). Anal. Calcd for $C_{14}H_{23}N_3O_2$, C, 63.37; H, 8.74; N, 15.84; Found: C, 63.36; H, 8.48; N, 15.84.

No. 6: ^{1}H-NMR δ 1.02 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 2.07 (s, 3H), 2.28 (s, 3H), 2.81 (m, 1H), 6.41 (d, J = 9.1 Hz, 1H), 7.9 (d, J = 9.1 Hz, 1H), 7.89−7.9 (bs, 2H); MS (CI) m/z 237.3 (M + H). Anal. Calcd for $C_{12}H_{19}N_3O_2$, C, 60.74; H, 8.07; N, 17.8; Found: C, 60.9; H, 8.01; N, 17.71.

No. 7: ^{1}H-NMR δ 0.86 (t, J = 7.3 Hz, 3H), 1.27 (sextet, 2H), 1.46 (quintet, 2H), 2.28 (s. 3H), 2.32 (t, J = 7.4 Hz, 2H), 3.54 (s, 2H), 6.43 (d, J = 8.8 Hz, 1H), 7.81 (bs, 2H), 7.92 (d, J = 8.8 Hz, 1H); MS (CI) m/z 252 (M + H).

No. 8: ^{1}H-NMR δ 1.20 (m, 5H), 1.60 (d, J = 12.5 Hz, 1H), 1.78 (m, 4H), 2.12 (s, 3H), 2.27 (s, 3H), 2.35 (m, 1H), 3.69 (s, 2H), 6.41 (d, J = 8.8 Hz, 1H), 7.89−7.91 (bs, 2H), 7.90 (d, J = 8.8 Hz, 3H); MS (CI) m/z 278 (M + H).

No. 9: ^{1}H-NMR δ 2.24 (s, 3H), 2.28 (s, 3H), 2.60 (d, J = 4.1 Hz, 2H), 3.64 (s, 2H), 3.82−3.86 (m, 2H), 3.88−3.97 (m, 2H), 4.97 (t, J = 4.1 Hz, 1H), 6.41 (d, J = 8.8 Hz, 1H), 7.67 (bs, 2H), 7.92 (d, J = 9 Hz, 1H); MS (CI) m/z 282 (M + H). Anal. Calcd for $C_{13}H_{19}N_3O_4$, C, 55.51; H, 6.81; N, 14.94; Found: C, 55.63; H, 6.77; N, 14.88.

No. 10: ^{1}H-NMR δ 1.18 (m, 6H), 1.65 (m, 3H), 1.91 (m, 2H), 2.29 (s, 3H), 2.44 (m, 1H), 3.87 (s, 2H), 6.43 (d, J = 8.8 Hz, 1H), 7.69 (bs, 2H), 7.91(d, J = 8.8 Hz, 1H); MS (CI) m/z 264 (M + H).

No. 11: ^{1}H-NMR δ 1.26 (m, 2H), 2.03 (quintet, 2H), 2.32 (s, 3H), 3.14 (t, J = 7.1 Hz, 2H), 3.62 (s, 2H), 6.46 (d, J = 8.8 Hz, 1H), 7.07 (bs, 2H), 7.98 (d, J = 8.8 Hz, 1H); MS (CI) m/z 222 (M + H).

No. 12: ^{1}H-NMR δ 7.91 (d, J = 8.8 Hz, 1H), 7.81 (bs, 2H), 6.42 (d, J = 8.8 Hz, 1H), 3.68 (s, 2H), 2.48 (m, 4H), 2.30 (s, 3H), 1.75 (m, 4H), MS: (CI) m/z 236 (M + H).

No. 13: ^{1}H-NMR δ 1.17 (d, J = 6.1 Hz, 1H), 1.37−1.45 (m, 1H), 1.6−1.68 (m, 2H), 1.93−2.01 (m, 1H), 2.08 (q, 1H), 2.3 (s, 3H), 2.35−2.42 (m, 1H), 2.77−2.82 (m, 1H), 6.42 (d, J = 8.8 Hz, 1H), 7.85 (bs, 2H), 7.9 (d, J = 8.8 Hz, 1H); MS (CI) m/z 250 (M + H).

No. 14: ^{1}H-NMR δ 0.97 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H), 1.29−1.42 (m, 2H), 1.81−1.9 (m, 2H), 2.32−1.42 (s, 3H), 2.57 (q, 2H), 3.71 (s, 2H), 6.41 (d, J = 8.8 Hz, 1H), 7.86 (bs, 2H), 7.90 (d, J = 8.8 Hz, 1H); MS (CI) m/z 264 (M + H). Anal. Calcd for $C_{13}H_{19}N_3O_2$, C, 63.85; H, 8.04; N, 15.96. Found: C, 63.82; H, 7.94; N, 15.83.

No. 15: ^{1}H-NMR δ 1.49 (m, 6H), 2.27 (s, 3H), 2.35 (bs, 4H), 3.52 (s, 2H), 6.42 (d, J = 9 Hz, 1H), 7.84 (bs, 2H), 7.91 (d, J = 9 Hz, 1H); MS (CI) m/z 250 (M + H). Anal. Calcd for $C_{13}H_{19}N_3O_2$, C, 62.63; H, 7.68; N, 16.85. Found: C, 62.75; H, 7.86; N, 16.62.

No. 16: ^{1}H-NMR δ 1.19 (d, J = 6.1 Hz, 3H), 1.41 (m, 5H), 1.64 (m, 2H), 1.91 (m, 1H), 2.27 (s, 3H), 2.63 (m, 1H), 3.33 (d, J = 13.2 Hz, 1H), 4.0 (d, J = 13.2 Hz, 1H), 6.41 (d, J = 9 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.95 (bs, 2H); MS (CI) m/z 264 (M + H).

No. 17: ^{1}H-NMR δ 0.88 (d, J = 6.6 Hz, 3H), 1.14 (m, 2H), 1.35 (m, 1H), 1.59 (d, 2H, J = 12.9 Hz), 1.95 (t, 2H, J = 11.6 Hz), 2.79 (d, 2H, J = 11.5 Hz), 3.53 (s, 2H), 6.42 (d, 1H, J = 9 Hz), 7.83 (bs, 2H), 7.91 (d, 1H, J = 8.8 Hz); MS (CI) m/z 264 (M + H). Anal. Calcd for $C_{14}H_{21}N_3O_2$, C, 63.85; H, 8.04; N, 15.96. Found: C, 64.27; H, 8.18; N, 15.89.

No. 18: ^{1}H-NMR δ 0.52 (q, 1H), 0.80 (d, 6H, J = 6.3 Hz), 1.27 (m, 1H), 1.46 (t, 1H, J = 10.9 Hz), 1.69 (m, 3H), 2.27 (s, 3H), 2.73 (d, 2H, J = 8.8 Hz), 3.52 (s, 2H), 6.43 (d, 1H, J = 8.8 Hz), 7.82 (bs, 2H), 7.92 (d, 1H, J = 8.8 Hz); MS (CI) m/z 278 (M + H). Anal. Calcd for $C_{15}H_{13}N_3O_2$, C, 64.96; H, 8.36; N, 15.15. Found: C, 64.87; H, 8.30; N, 14.88.

No. 19: ^{1}H-NMR δ 2.34 (s, 3H), 2.37−2.48 (m, 4H), 3.63 (s, 3H), 3.71−3.73 (m, 4H), 6.49 (d, 1H, J = 8.8 Hz), 7.65 (bs, 2H), 7.98 (d, 1H, J = 8.8 Hz); MS (CI) m/z 252 (M + H). Anal. Calcd for $C_{12}H_{17}N_3O_3$, C, 57.36; H, 6.82; N, 16.72; Found: C, 57.72; H, 6.98; N, 16.5.

No. 20: ^{1}H-NMR δ 2.28 (s, 3H), 2.62−2.63 (m, 4H), 2.64−2.69 (m, 4H), 3.58 (s, 2H), 6.45 (d, J = 9 Hz, 1H), 7.58 (bs, 2H), 7.94 (d, J = 8.9 Hz, 1H); MS (CI) m/z 268 (M + H). Anal. Calcd for $C_{12}H_{17}N_3O_2S$, C, 53.93; H, 6.36; N, 15.73. Found: C, 53.57; H, 6.36; N, 15.29.

No. 21: ^{1}H-NMR δ 2.09 (s, 3H), 2.25 (s, 3H), 2.35 (m, 8H), 3.51 (s, 2H), 6.49 (d, 1H, J = 8.8 Hz), 7.62 (bs, 2H), 7.80 (d, 1H, J = 8.8 Hz); MS (CI) m/z 265 (M + H).

No. 22: ^{1}H-NMR δ 1.57 (bs, 8H), 2.27 (s, 3H), 2.54 (m, 4H), 3.64 (s, 2H), 6.42 (d, 1H, J = 8.8 Hz), 7.91 (d, 1H, J = 8.8 Hz), 7.95 (bs, 2H); MS (CI) m/z 264 (M + H).

No. 23: ^{1}H-NMR δ 0.84−0.97 (m, 3H), 1.06−1.24 (m, 4H), 1.45−1.68 (m, 6H), 1.92−1.99 (m, 1H), 2.63−2.66 (m, 1H), 2.82−2.85 (m, 1H), 3.52 (s, 3H), 6.42 (d, 1H, J = 8.8 Hz), 7.84 (bs, 2H), 7.91 (d, 1H, J = 8.8 Hz); MS (CI) m/z 304 (M + H).

No. 24: ^{1}H-NMR δ 0.94−1.87 (m, 4H), 2.26 (s, 3H), 2.26 (s, 3H), 2.25−2.3 (m, 1H), 2.67−2.71 (m, 1H), 3.22 (d, 1H, J = 13.2 Hz), 4.10 (d, 1H, J = 13.2 Hz), 6.40 (d, 1H, 8.8 Hz), 7.89 (d, 1H, 8.8 Hz), 7.94 (bs, 2H); MS (CI) m/z 304 (M + H).

2-Amino-6-methyl-3-nitrobenzyl Bromide (3). To a mixture of PPh_3 (1.729 g, 6.6 mmol) and CBr_4 (2.18 g, 6.6 mmol) in anhydrous ether (50 mL) was added 2-amino-6-methyl-3-nitrobenzyl alcohol (**1**) (1.092 g, 6 mmol) with vigorous stirring at rt. The reaction was monitored by TLC (SiO_2, petroleum ether/EtOAc, 1:1). On completion, the supernatant was decanted and the yellow residue triturated with additional ether (2 × 100 mL). The ether extracts were combined and evaporated to give a sticky orange solid (4.43 g). The crude material was purified by flash column chromatography (SiO_2, petroleum ether/EtOAc, 9:1 to 8:2). The product was isolated as a yellow solid (0.925 g, 63%) and used immediately for coupling with the amines. The product was unstable at rt and under N_2 atmosphere and on storage gave a polar orange residue.

General Procedure for Synthesis of Benzylamines from Benzyl Bromide. Synthesis of 2-Amino-6-methyl-3-nitro-*N*,*N*-diisopropylbenzylamine (Table 1, no. 5). To a solution of benzyl bromide (0.925 g, 3.77 mmol) in anhydrous THF (5 mL) was added diisopropylamine (2 mL, 25 mmol) with stirring. The reaction mixture was stirred overnight and filtered. The filtrate was evaporated to dryness and extracted with EtOAc (2 × 50 mL). The EtOAc extracts were washed with water and dried over $MgSO_4$. The product was purified by column chromatography (SiO_2, petroleum ether/EtOAc, 1:1) and isolated as a yellow solid (0.811g 82%): ^{1}H-NMR δ 1.10 (d, 12H, J = 6.6 Hz), 2.34 (s, 3H), 3.03 (septet, 2H), 3.82 (s, 2H), 6.43 (d, 1H, J = 8.8 Hz), 7.92 (d, 1H, J = 9.0 Hz), 8.15 (bs, 2H); MS (CI) m/z 266 (M + H). Anal. Calcd for $C_{14}H_{23}N_3O_2$, C, 63.37; H, 8.74; N, 15.84; Found: C, 63.36; H, 8.48; N, 15.84.

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Supporting Information Available: Copies of ^{1}H-NMR (400 MHz) spectra of new compounds (Table 1, entries 1−24, and Table 2, entries 4, 5, and 7) (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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