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Gold(III)/Sodium Diphenylphosphinobenzene-3-sulfonate (TPPMS) Catalyzed Dehydrative N-Benzylation of Electron-Deficient Anilines in Water

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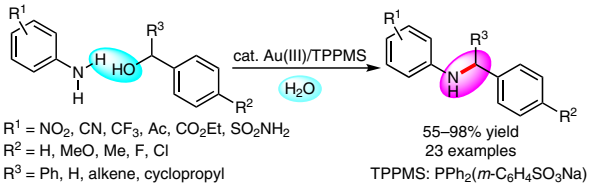

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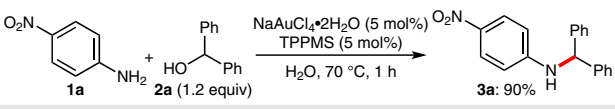
Abstract A strategy for the dehydrative N-benzylation of electron-deficient anilines in water has been developed. The gold(III)/sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) catalyst is highly effective as a Lewis acid for the activation of alcohols and tolerates aerobic conditions. A Hammett study in the reaction of *para*-substituted benzhydryl alcohols shows negative σ values, indicating a build-up of cationic charge during the rate-determining sp^3 C–O bond-cleavage step. The inverse kinetic solvent isotope effect (KSIE = 0.6) is consistent with a specific acid catalysis mechanism. This simple protocol can be performed under mild conditions in an atom-economic process without the need for base or other additives, furnishing the electron-deficient *N*-benzylic anilines in moderate to excellent yields along with water as a sole coproduct.

Key words gold, water, benzylic alcohol, aniline, N-benzylation

The gold-catalyzed dehydrative substitution reaction of alcohols with amines affords the desired products along with water as the sole coproduct. This reaction has emerged as a powerful methodology for the formation of C–N bonds due to the advantages of being a salt-free and atom-economical process that does not transform the hydroxyl group into a good leaving group.[1,2] In 2005, the pioneering work of Campagne demonstrated the nucleophilic substitution of propargylic alcohols using the $NaAuCl_4{\cdot}2H_2O$ catalyst, which activated the alcohols through coordination with the π-bond.[3] Campagne and Prim et al. developed the direct catalytic amination of benzylic alcohols with poor amine nucleophiles.[4] Such efficiency is mainly due to the Lewis acidic character of the gold(III) catalyst for the activation of several sp^3 C–O bonds, thus promoting unique chemical transformations.[5] While these are green and sustainable strategies for direct functionalization of organic molecules due to their advantages in atom economy, the use of hazardous organic solvents such as CH_2Cl_2 or $ClCH_2CH_2Cl$ under extrusion of moisture conditions is generally required. Recently, the Wang group developed a gold-catalyzed borrowing-hydrogen reaction in good yields with high chemoselectivity under wet conditions.[5c] Therefore, developing more efficient and environmentally friendly protocols is highly desirable due to the scope of applications and industrial utility.[6,7]

Water is widely recognized as a greener solvent alternative for organic synthesis because of its universal abundance, nontoxicity and environmental compatibility.[8,9] We have been developing a strategy for dehydrative substitution of alcohols catalyzed by $NaAuCl_4{\cdot}2H_2O$ and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) in water.[10] Recently, we described the first example of a selective N-benzylation of water-soluble substrates such as unprotected anthranilic acids.[10c] As an extension of our investigation, we herein report a strategy for the catalytic dehydrative N-benzylation of electron-deficient anilines. To our knowledge, this is the first report of a gold-catalyzed direct modification of nitroanilines under mild reaction conditions in water without the need for base or other additives (Scheme 1). Notably, the gold(III)/TPPMS catalyst is highly effective as a Lewis acid for the activation of alcohols, while common Lewis or Brønsted acid such as Cu(II),[11] Co(II),[12] or Fe(III) were ineffective for dehydrative N-benzylation of 4-nitroaniline (**1a**) (see Table 1).



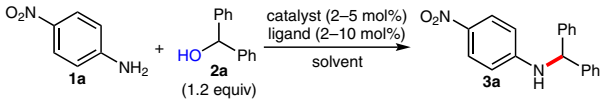
Scheme 1 Catalytic dehydrative N-benzylation of 4-nitroaniline (**1a**)

Initially, 4-nitroaniline (**1a**) and benzhydrol (**2a**) were chosen as model compounds to optimize the dehydrative amination. The desired product **3a** was obtained in 63% yield when using $NaAuCl_4{\cdot}2H_2O$ (2 mol%) and TPPMS **L1** (2 mol%) in water at 40 °C for 16 hours (Table 1, entry 1). A control experiment using HCl indicated that the gold(III) catalyst played a crucial role in the catalytic system (entry 2). Furthermore, no reaction occurred when using only $NaAuCl_4{\cdot}2H_2O$ catalyst (entry 3). The yield of **3a** was increased to 90% in a shorter reaction time when using $NaAuCl_4{\cdot}2H_2O$ (5 mol%) and TPPMS (5 mol%) at 70 °C (entry 4). Increasing the amount of the TPPMS ligand resulted in a slightly lower yield (entry 5). With regard to the gold catalysts, $NaAuCl_4{\cdot}2H_2O$ gave the best result (entry 4 vs. entries 6–9). Other water-soluble phosphine ligands **L2–7** resulted in no reaction or lower yields (entries 10–15).[13] Other chloride salts such as Cu(II), Co(II) or Fe(III) were less effective than $NaAuCl_4{\cdot}2H_2O$ (entries 16–18). Organic solvents such as EtOH, DMF, 1,4-dioxane or CH_2Cl_2 were not suitable compared with water in our catalytic system (entries 19–22).

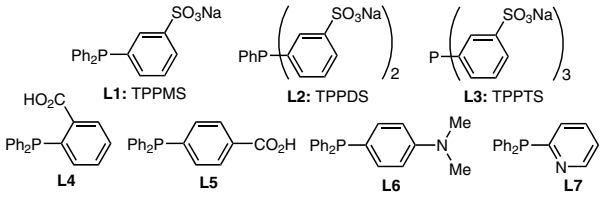
With the optimized conditions in hand, we examined the substrate scope of the dehydrative amination (Scheme 2). First, the scope of benzylic alcohols **2** with 4-nitroaniline (**1a**) as the coupling partner was examined. As expected, both electron-donating (OMe and Me) and electron-withdrawing (Cl and F) groups on the benzene ring of substituted benzhydrols **2** were well tolerated, and the corresponding N-benzylated products **3b–f** were formed in moderate to excellent yields (72–89%). In contrast, decafluorobenzhydrol failed to react under the same conditions, suggesting that stability of the diarylcarbocation was critical to the success of the reaction. We explored the direct amination of the hydroxyl group of π-activated alcohols such as *trans*-1,3-diphenyl-2-propen-1-ol, which afforded the corresponding product **3g** in 86% yield. Furthermore, a simple benzylic alcohol such as 4-methoxybenzylalcohol could be transformed into **3h** in 70% yield.

Encouraged by these results, we next examined the scope of electron-deficient anilines **1** with benzhydrol (**2a**) as the coupling partner. Various nitroanilines **1** showed good reactivities, regardless of whether they had electron-donating or -withdrawing substituents (72–98%, **3i–q**). The carbon–bromine moiety in **3n** was left intact, which could be employed for further cross-coupling. Furthermore, replacement of the NO_2 group with several electron-withdrawing groups (CN, CF_3, Ac and CO_2Et) was also tolerated to produce the corresponding N-benzylated products **3r–u** (55–83%). In contrast, electron-sufficient 4-anisidine did not react due to poisoning of the Lewis acidic gold(III) catalyst. A sterically demanding 4-nitro-1-naphthylamine (**1b**) led to the corresponding N-benzylated **3v** along with C-benzylated **4** in 67% and 20% yields, respectively (Scheme 3). Ghorai et al. reported the dehydrative Friedel–Crafts benzylation of 4-nitroaniline via Hofmann–Martius rearrangement catalyzed by Re_2O_7. Therefore, the benzyl cation species would be generated from **3v** followed by the formation of *ortho*-benzylated aniline **4** in our catalytic system.[14]

Table 1 Optimization of Reaction Conditions[a]

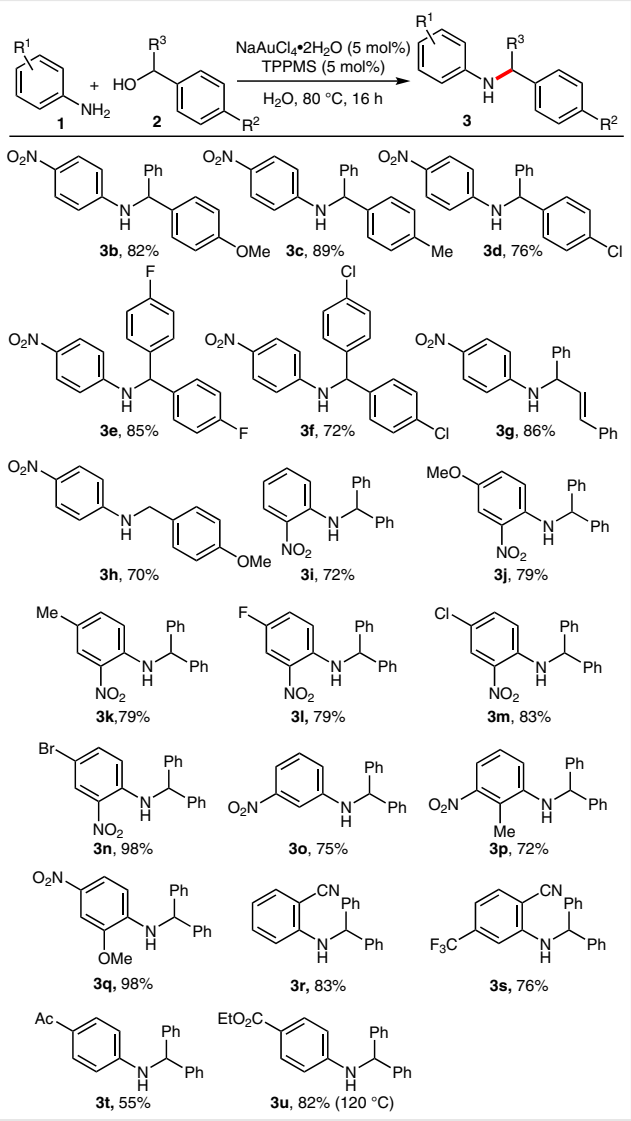


Entry	Cat. (mol%)	Ligand (mol%)	*T* (°C)	*t* (h)	Solv.	Yield (%)[b]
1	$NaAuCl_4{\cdot}2H_2O$ (2)	**L1** (2)	40	16	H_2O	63
2	HCl (2)	none	40	16	H_2O	trace
3	$NaAuCl_4{\cdot}2H_2O$ (2)	none	40	16	H_2O	trace
4	$NaAuCl_4{\cdot}2H_2O$ (5)	**L1** (5)	70	1	H_2O	90
5	$NaAuCl_4{\cdot}2H_2O$ (5)	**L1** (10)	70	1	H_2O	84
6	AuCl (5)	**L1** (5)	70	1	H_2O	62
7	$HAuCl_4{\cdot}3H_2O$ (5)	**L1** (5)	70	1	H_2O	49
8	$AuBr_3$ (5)	**L1** (5)	70	1	H_2O	62
9	$AuCl_3$ (5)	**L1** (5)	70	1	H_2O	0
10	$NaAuCl_4{\cdot}2H_2O$ (5)	**L2** (5)	70	1	H_2O	14
11	$NaAuCl_4{\cdot}2H_2O$ (5)	**L3** (5)	70	1	H_2O	12
12	$NaAuCl_4{\cdot}2H_2O$ (5)	**L4** (5)	70	1	H_2O	trace
13	$NaAuCl_4{\cdot}2H_2O$ (5)	**L5** (5)	70	1	H_2O	trace
14	$NaAuCl_4{\cdot}2H_2O$ (5)	**L6** (5)	70	1	H_2O	trace
15	$NaAuCl_4{\cdot}2H_2O$ (5)	**L7** (5)	70	1	H_2O	trace
16	$CuCl_2$ (5)	**L1** (5)	70	1	H_2O	27
17	$CoCl_2{\cdot}6H_2O$ (5)	**L1** (5)	70	1	H_2O	0
18	$FeCl_3$ (5)	**L1** (5)	70	1	H_2O	38
19	$NaAuCl_4{\cdot}2H_2O$ (5)	**L1** (5)	70	1	EtOH	trace
20	$NaAuCl_4{\cdot}2H_2O$ (5)	**L1** (5)	70	1	DMF	trace
21	$NaAuCl_4{\cdot}2H_2O$ (5)	**L1** (5)	70	1	dioxane	48
22	$NaAuCl_4{\cdot}2H_2O$ (5)	**L1** (5)	50	16	CH_2Cl_2	48

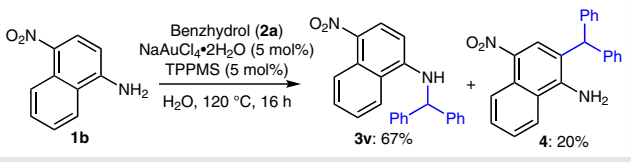


[a] Reaction conditions: 4-nitroaniline (**1a**) (1 mmol), catalyst (2 or 5 mol%), ligand (2 or 5 mol%), benzhydrol (**2a**) (1.2 equiv), solvent (4 mL), in a sealed tube under air.
[b] The yield was determined by ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard.

To demonstrate the electronic effect of the substituents on the rates of the sp^3 C–O bond cleavage of alcohols and the C–N bond-formation reaction, Hammett studies were conducted on the gold-catalyzed dehydrative amination.[15] First, the relative rates of coupling of 4-substituted 2-nitroanilines **1** (X = OMe, Me, H, F, and Br groups) with benzhydrol (**2a**) were examined. Scheme 4A shows no correla-

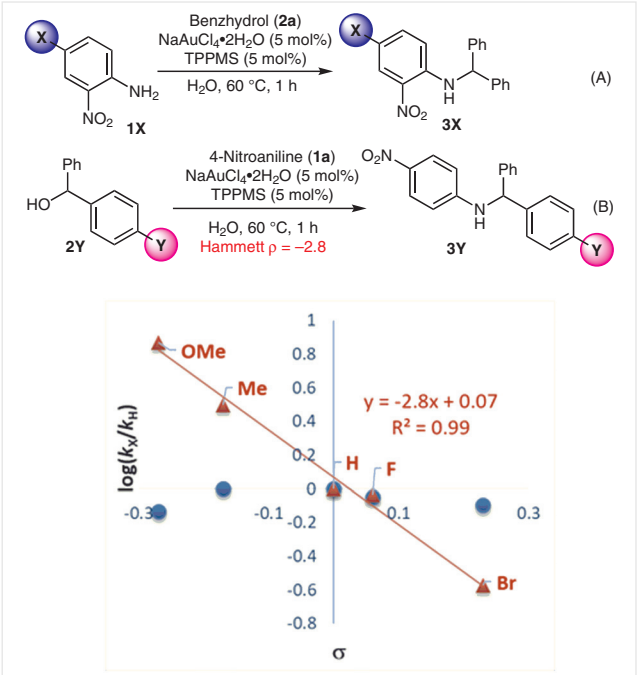


Scheme 2 Scope of electron-deficient anilines **1** and benzylic alcohols **2**. *Reagents and conditions*: **1** (1 mmol), $NaAuCl_4{\cdot}2H_2O$ (5 mol%), TPPMS (5 mol%), alcohol **2** (1.2 mmol), H_2O (4 mL), 80 °C, 16 h in a sealed tube under air. Yield of isolated product.



Scheme 3 The benzylation of 4-nitro-1-naphthylamine (**1b**)

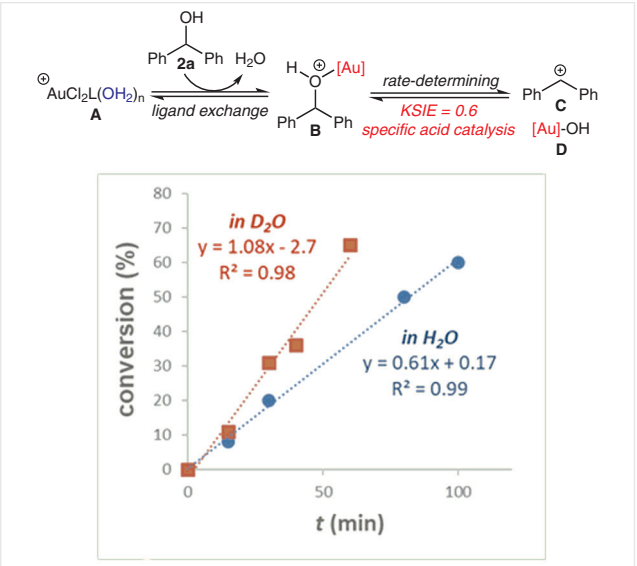
tion of the substituent constant parameter, indicating that the reaction is not sensitive to substituents and no charge is developed on the anilines in the transition state. Next, the relative rates of the reaction between 4-nitroaniline (**1a**) and *para*-substituted benzhydryl alcohols **2** (Y = OMe, Me, H, F, and Br groups) were examined. Scheme 4B shows excellent correlation (R^2 = 0.99) between the log (k_X/k_H) and the σ value of the respective substituents that resulted in a negative ρ value of 2.8. This result indicates a build-up of positive charge in the transition state.



Scheme 4 Hammett plots for the reaction of (A) 4-substituted 2-nitroanilines **1** (X = OMe, Me, H, F, and Br groups) (circles) and (B) 4-substituted benzhydryl alcohols **2** (Y = OMe, Me, H, F, and Br groups) (triangles).

To gain insight into the catalytic sp^3 C–O bond-activation step, we carried out kinetic isotope effect (KIE) experiments. The reactions of 4-nitroaniline (**1a**) with benzhydrol (**2a**) were monitored by ^1H NMR spectroscopy to determine the zero-order kinetics for construction of **3a** (Scheme 5). The rate of reaction was 1.8 times greater in D_2O than in H_2O with an inverse kinetic solvent isotope effect (KSIE: kH_2O/kD_2O) of 0.6,[16] indicating a specific acid catalysis mechanism as follows. Aqua complex **A** with alcohol **2a** is in a fast equilibrium with its Lewis acid adduct (conjugate acid) **B**. The rate-determining step involving the sp^3 C–O bond cleavage occurs via **B** to form the benzyl cation species **C**.[17] Since the overall rate of the reaction depends only on the activation of alcohol **2a** catalyzed by complex **A**, species **B** should form more slowly in H_2O than in D_2O. This is explained by the fact that hydrogen bonds of H_2O would be better at solvating gold cation **A**, which makes it less able to activate alcohol **2a** in H_2O than in D_2O. Soper et al. investigated the structures of light and heavy water with X-ray diffraction and found that the OH bond length in H_2O is 3% longer than the OD bond length in D_2O.[18] Harada et al. reported that the vibration profile of pre-edge excited HDO

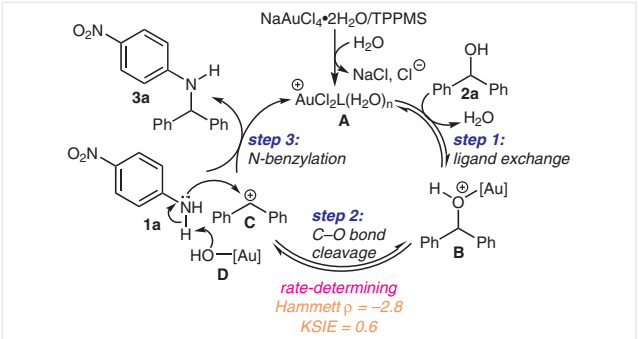
water has a greater OH-stretch contribution compared with OD, which supports the preference for OH being the weakened or broken hydrogen bond.[19]



Scheme 5 Comparison of the reaction of 4-nitroaniline (**1a**) with benzhydrol (**2a**) 'in H_2O' (circles) and 'in D_2O' (squares) at 60 °C

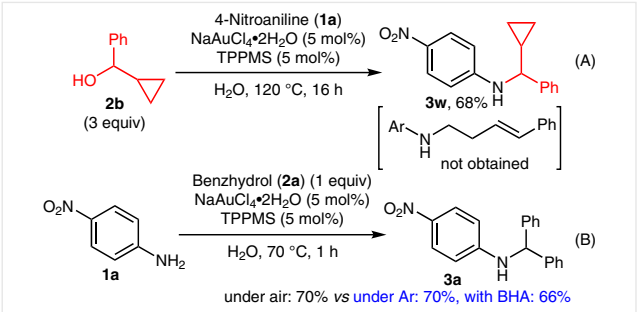
Based on these results and on previous reports, the following mechanism can be suggested (Scheme 6). Initially, the treatment of $NaAuCl_4{\cdot}2H_2O$ with water-soluble phosphine ligand TPPMS generates an aqua complex **A**. Subsequently, the Lewis acidic gold(III) cation **A** coordinates with the oxygen atom of alcohol **2a** to form intermediate **B** (Step 1: ligand exchange), and sp^3 C–O bond activation occurs to generate the benzylic cation **C** (Step 2: C–O bond cleavage). The observed negative Hammett ρ value of 2.8 in the reaction of *para*-substituted benzhydryl alcohols **2** clearly shows cationic charge build-up during the rate-determining sp^3 C–O bond-cleavage step (see Scheme 4B). Furthermore, the inverse kinetic solvent isotope effect (KSIE) of 0.6 is consistent with the specific acid catalysis mechanism (see Scheme 5). Next, the hydroxyl anion of gold species **D** acts as a base to remove the acidic proton of substrate **1a**, which attacks the electrophilically active benzyl cation **C** to afford the corresponding N-benzylated product **3a** (Step 3: N-benzylation).

Several control experiments were performed to examine the possibility of a radical pathway based on a single-electron transfer (SET). First, radical clock experiments using α-cyclopropylbenzyl alcohol (**2b**) were conducted to observe the rapid isomerization of the cyclopropylmethyl radical to the allylmethyl radical, which is well known in free-radical chemistry (Scheme 7A). As expected, corresponding **3w** was obtained in 68% isolated yield via the cyclopropylmethyl cation and not the ring-opened product. Next, in the presence of a radical scavenger (BHA: 3-*tert*-



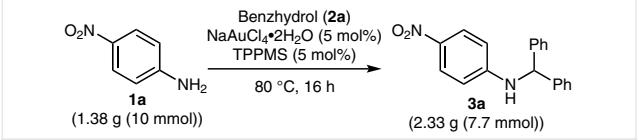
Scheme 6 Proposed mechanism

butyl-4-hydroxyanisole, 1 equiv) or under an Ar atmosphere, the yield of the desired product **3a** remained unchanged (Scheme 7B). These results suggest that a radical pathway based on a SET is not involved in this catalytic system.



Scheme 7 Control experiments

Finally, to demonstrate the synthetic utility of our catalytic system, a gram-scale reaction of substrate **1a** with alcohol **2a** in the presence of gold(III)/TPPMS catalyst in water was carried out (Scheme 8). After 16 h, the reaction mixture was extracted with EtOAc, then crude product **3a** was purified simply by recrystallization from *n*-hexane and EtOAc to give desired **3a** in 77% isolated yield. The developed process avoids the use of column chromatography.



Scheme 8 Scale-up experiment

In summary, we have reported an environmentally benign protocol for the direct dehydrative amination of benzylic alcohols using a water-soluble gold(III)/TPPMS catalyst in water. This catalytic system is applicable for the direct modification of electron-deficient anilines and proceeds in moderate to excellent yields. This greener method has reduced waste generation, uses safer solvents and reaction

conditions, and increases energy efficiency, all of which contribute to the efficiency of a chemical transformation. Moreover, this reaction can be easily amplified to a gram level without the use of column chromatography for purification. Therefore, this strategy has emerged as an attractive alternative to traditional synthetic methods.

All of the starting materials and solvents were purchased from Sigma–Aldrich Japan (Tokyo, Japan), FUJIFILM Wako Pure Chemical Co. (Osaka, Japan), and TCI Co., Ltd. (Tokyo, Japan). All commercially available reagents and solvents were used without further purification. CHROMATOREX Q-PACK SI50 (Fuji Silysia Chemical Ltd, Japan) was used for flash column chromatography. All melting points were determined using a Yanako micro melting point apparatus without correction. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL ECS400 spectrometer. IR spectra were measured with a JASCO FT/IR-4100 spectrometer. Mass spectra were obtained using a JEOL the JMS-700 MStation Mass Spectrometer.

General Procedure

A mixture of aniline **1** (1 mmol), $NaAuCl_4{\cdot}2H_2O$ (20 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) (18 mg, 0.05 mmol) and benzylic alcohol **2** (1.2 mmol) in H_2O (4 mL) was heated at 80 °C for 16 h in a sealed tube under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product **3**.

N-Benzhydryl-4-nitroaniline (3a)[11]

By following the scale-up experiment procedure (Scheme S5), **3a** was obtained.

Yield: 2.34 g (77%); pale-yellow solid; mp 178–181 °C.

IR (KBr): 3407, 1602, 1513 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.01 (br s, 1 H), 5.63 (s, 1 H), 6.51 (d, *J* = 9.2 Hz, 2 H), 7.25–7.38 (m, 10 H), 8.03 (d, *J* = 9.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 60.2, 111.9, 125.9, 127.3, 127.4, 128.6, 136.3, 141.9, 153.6.

MS (FAB): *m*/*z* = 305 [M + H]$^+$.

N-[(4-Methoxyphenyl)(phenyl)methyl]-4-nitroaniline (3b)[4]

By following the general procedure, **3b** was obtained.

Yield: 273 mg (82%); yellow solid; mp 120–123 °C.

IR (KBr): 3408, 1602, 1515 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.97 (br d, *J* = 4.6 Hz, 1 H), 5.59 (d, *J* = 4.8 Hz, 1 H), 6.50 (d, *J* = 9.2 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.27–7.83 (m, 5 H), 8.02 (d, *J* = 9.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.1, 59.6, 111.9, 114.0, 125.9, 127.2, 127.3, 128.6, 133.9, 136.2, 142.3, 153.6, 158.5.

MS (FAB): *m*/*z* = 335 [M + H]$^+$.

4-Nitro-*N*-[phenyl(*p*-tolyl)methyl]aniline (3c)

By following the general procedure, **3c** was obtained.

Yield: 283 mg (89%); yellow solid; mp 131–134 °C.

IR (KBr): 3408, 1600, 1513 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 4.97 (br d, *J* = 4.8 Hz, 1 H), 5.59 (d, *J* = 4.8 Hz, 1 H), 6.50 (d, *J* = 9.2 Hz, 2 H), 7.15–7.20 (m, 4 H), 7.27–7.38 (m, 5 H), 8.03 (d, *J* = 9.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.6, 60.0, 111.9, 125.9, 127.2, 127.3, 127.4, 128.6, 129.2, 136.2, 136.5, 138.9, 142.1, 153.6.

MS (FAB): *m*/*z* = 319 [M + H]$^+$.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.41; H, 5.79; N, 8.63.

N-[(4-Chlorophenyl)(phenyl)methyl]-4-nitroaniline (3d)[4]

By following the general procedure, **3d** was obtained.

Yield: 258 mg (76%); yellow solid; mp 138–140 °C.

IR (KBr): 3371, 1599, 1531 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 (brd, *J* = 4.6 Hz, 1 H), 5.60 (d, *J* = 4.8 Hz, 1 H), 6.50 (d, *J* = 9.2 Hz, 2 H), 7.24–7.40 (m, 9 H), 8.04 (d, *J* = 9.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 59.4, 112.0, 125.9, 127.4, 127.5, 128.6, 128.7, 129.3, 131.9, 136.5, 140.9, 141.5, 153.4.

MS (FAB): *m*/*z* = 339 [M + H]$^+$.

N-[Bis(4-fluorophenyl)methyl]-4-nitroaniline (3e)[20]

By following the general procedure, **3e** was obtained.

Yield: 291 mg (85%); yellow powder; mp 123–125 °C.

IR (KBr): 3401, 1604, 1510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.61 (s, 1 H), 6.50 (d, *J* = 9.2 Hz, 2 H), 7.06 (dd, *J* = 8.5, 8.5 Hz, 4 H), 7.26 (dd, *J* = 7.1, 7.1 Hz, 4 H), 8.05 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.6, 115.5 (d, J_{CF} = 22.0 Hz), 125.9, 129.4 (d, J_{CF} = 7.7 Hz), 136.5, 138.0 (d, J_{CF} = 3.8 Hz), 153.3, 161.4 (d, J_{CF} = 244.4 Hz); MS (FAB): *m*/*z* = 341 [M + H]$^+$.

N-[Bis(4-chlorophenyl)methyl]-4-nitroaniline (3f)[20]

By following the general procedure, **3f** was obtained.

Yield: 268 mg (72%); yellow solid; mp 191–192 °C.

IR (KBr): 3402, 1605, 1520 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (br d, *J* = 4.8 Hz, 1 H), 5.58 (d, *J* = 4.8 Hz, 1 H), 6.49 (d, *J* = 9.1 Hz, 2 H), 7.21–7.36 (m, 8 H), 8.04 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.7, 112.1, 125.9, 128.7, 129.3, 132.1, 136.6, 140.5, 153.3.

MS (FAB): *m*/*z* = 373 [M + H]$^+$.

(*E*)-*N*-(1,3-Diphenylallyl)-4-nitroaniline (3g)[20]

By following the general procedure, **3g** was obtained.

Yield: 285 mg (86%); yellow solid; mp 144–146 °C.

IR (KBr): 3377, 1600, 1530 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.88 (br d, *J* = 5.5 Hz, 1 H), 5.21 (t, *J* = 5.7 Hz, 1 H), 6.38 (dd, *J* = 15.8, 6.0 Hz, 1 H), 6.55–6.62 (m, 3 H), 7.29–7.41 (m, 10 H), 8.06 (d, *J* = 9.2 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 58.5, 111.8, 126.0, 126.4, 127.1, 127.4, 127.8, 128.6, 128.7, 130.0, 130.4, 136.1, 136.2, 141.3, 153.4.

MS (FAB): *m*/*z* = 331 [M + H]$^+$.

***N*-(4-Methoxybenzyl)-4-nitroaniline (3h)**[21]

By following the general procedure, **3h** was obtained.

Yield: 181 mg (70%); yellow solid; mp 135–137 °C.

IR (KBr): 3357, 1598, 1511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 4.35 (s, 2 H), 6.57 (d, *J* = 9.2 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 8.09 (d, *J* = 9.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 45.4, 55.1, 111.3, 113.9, 126.2, 128.6, 130.3, 135.8, 154.4, 158.4.

MS (FAB): *m*/*z* = 259 $[M + H]^+$.

***N*-Benzhydryl-2-nitroaniline (3i)**[7a]

By following the general procedure, **3i** was obtained.

Yield: 219 mg (72%); brown solid; mp 98–100 °C.

IR (KBr): 3382 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.60 (d, *J* = 3.7 Hz, 1 H), 5.57 (d, *J* = 4.5 Hz, 1 H), 6.80 (dd, *J* = 8.1, 2.4 Hz, 1 H), 7.50 (ddd, *J* = 8.1, 1.7, 0.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.0, 115.2, 116.0, 126.8, 127.2, 127.9, 129.1, 132.5, 136.1, 141.3, 144.2.

MS (EI): *m*/*z* = 304 $[M + H]^+$.

***N*-Benzhydryl-4-methoxy-2-nitroaniline (3j)**

By following the general procedure, **3j** was obtained.

Yield: 264 mg (79%); brown solid; mp 144–146 °C.

IR (KBr): 3372, 1541, 1518 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3 H), 5.71 (d, *J* = 5.5 Hz, 1 H), 6.69 (d, *J* = 9.4 Hz, 1 H), 7.01 (dd, *J* = 9.3, 3.2 Hz, 1 H), 7.26–7.36 (m, 10 H), 7.65 (d, *J* = 3.0 Hz, 1 H), 8.51 (br d, *J* = 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.6, 60.4, 106.8, 117.1, 126.8, 126.9, 127.6, 129.0, 130.9, 139.5, 142.0, 149.6.

MS (FAB): *m*/*z* = 335 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.87; H, 5.46; N, 8.32.

***N*-Benzhydryl-4-methyl-2-nitroaniline (3k)**

By following the general procedure, **3k** was obtained.

Yield: 252 mg (79%); pale-yellow solid; mp 123–126 °C.

IR (KBr): 3382, 1631, 1567, 1525 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 5.72 (d, *J* = 5.5 Hz, 1 H), 6.63 (d, *J* = 8.7 Hz, 1 H), 7.01 (dd, *J* = 9.3, 3.2 Hz, 1 H), 7.26–7.39 (m, 10 H), 7.65 (d, *J* = 3.0 Hz, 1 H), 8.51 (br d, *J* = 5.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.4, 60.3, 115.6, 125.2, 125.5, 126.6, 126.8, 127.6, 128.5, 129.0, 131.4, 137.9, 141.9, 142.0.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_2O_2$: 319.1447; found: 319.1447.

***N*-Benzhydryl-4-fluoro-2-nitroaniline (3l)**

By following the general procedure, **3l** was obtained.

Yield: 255 mg (79%); pale-yellow solid; mp 116–119 °C.

IR (KBr): 3379, 1578, 1523 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.70 (d, *J* = 5.5 Hz, 1 H), 6.70 (dd, *J* = 9.6, 4.6 Hz, 1 H), 7.11 (ddd, *J* = 9.6, 7.3, 3.0 Hz, 1 H), 7.27–7.38 (m, 10 H), 7.92 (dd, *J* = 9.2, 2.8 Hz, 1 H), 8.49 (br d, *J* = 4.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.5, 112.2 (d, J_{CF} = 25.9 Hz), 116.6 (d, J_{CF} = 6.7 Hz), 124.9 (d, J_{CF} = 23.0 Hz), 127.3, 128.2, 129.3, 131.5 (d, J_{CF} = 7.7 Hz), 141.2, 141.4, 142.3, 152.9 (d, J_{CF} = 239.6 Hz).

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{15}FN_2O_2$: 323.1196; found: 323.1196.

***N*-Benzhydryl-4-chloro-2-nitroaniline (3m)**

By following the general procedure, **3m** was obtained.

Yield: 281 mg (83%); pale-yellow solid; mp 136–138 °C.

IR (KBr): 3372, 1610, 1564 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.71 (d, *J* = 5.5 Hz, 1 H), 6.68 (d, *J* = 9.2 Hz, 1 H), 7.23–7.39 (m, 11 H), 8.20 (d, *J* = 2.5 Hz, 1 H), 8.57 (br d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 60.3, 117.4, 119.5, 125.0, 126.8, 127.7, 129.0, 131.8, 136.2, 141.5, 142.6.

MS (EI): *m*/*z* (%) = 338 (37) $[M]^+$, 340 (21) $[M^+ + 2]$, 165 (100).

Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.65; H, 4.57; N, 8.05.

***N*-Benzhydryl-4-bromo-2-nitroaniline (3n)**

By following the general procedure, **3n** was obtained.

Yield: 377 mg (98%); pale-yellow solid; mp 130–132 °C.

IR (KBr): 3377, 1614, 1560 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.70 (d, *J* = 5.5 Hz, 1 H), 6.63 (d, *J* = 9.2 Hz, 1 H), 7.28–7.39 (m, 11 H), 8.34 (d, *J* = 2.5 Hz, 1 H), 8.57 (br d, *J* = 5.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.3, 107.4, 117.1, 127.3, 128.2, 128.5, 129.0, 129.3, 138.9, 140.9, 143.2.

MS (FAB): *m*/*z* 383 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{16}N_2O_2Br$: 383.0395; found: 383.0395.

***N*-Benzhydryl-3-nitroaniline (3o)**[22]

By following the general procedure, **3o** was obtained.

Yield 229 mg (75%); yellow solid; mp 111–113 °C.

IR (KBr): 3386 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.74 (d, *J* = 5.5 Hz, 1 H), 6.66 (ddd, *J* = 9.1, 7.2, 1.3 Hz, 1 H), 6.72 (d, *J* = 8.6 Hz, 1 H), 8.20 (dd, *J* = 8.6, 1.6 Hz, 1 H), 8.61 (d, *J* = 5.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.8, 107.6, 112.3, 119.0, 127.2, 127.9, 129.1, 132.5, 136.5, 141.3, 144.2.

MS (EI): *m*/*z* = 304 $[M + H]^+$.

***N*-Benzhydryl-2-methyl-3-nitroaniline (3p)**

By following the general procedure, **3p** was obtained.

Yield: 228 mg (72%); brown solid; mp 95–97 °C.

IR (KBr): 3383 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.54 (d, *J* = 4.5 Hz, 1 H), 5.64 (d, *J* = 5.2 Hz, 1 H), 6.32 (d, *J* = 8.8 Hz, 1 H), 7.65 (d, *J* = 2.2 Hz, 1 H), 7.75 (dd, *J* = 8.8, 2.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 63.0, 112.5, 114.7, 115.5, 126.9, 127.4, 127.8, 129.0, 141.9, 146.2, 151.5.

MS (EI): *m*/*z* = 318 $[M + H]^+$.

N-Benzhydryl-2-methoxy-4-nitroaniline (3q)

By following the general procedure, **3q** was obtained.

Yield: 329 mg (98%); yellow solid; mp 159–161 °C.

IR (KBr): 3418, 1594, 1498, 1329 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.94 (s, 3 H), 5.96 (d, *J* = 7.1 Hz, 1 H), 6.39 (d, *J* = 7.1 Hz, 1 H), 6.57 (d, *J* = 8.9 Hz, 1 H), 7.28 (tt, *J* = 7.1, 1.4 Hz, 2 H), 7.36 (dt, *J* = 7.1, 1.8 Hz, 4 H), 7.41 (dt, *J* = 6.9, 1.6 Hz, 4 H), 7.62 (d, *J* = 2.3 Hz, 1 H), 7.75 (dd, *J* = 8.9, 2.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.6, 60.6, 105.1, 108.8, 119.8, 127.8, 128.0, 129.2, 137.0, 142.3, 143.7, 145.9.

MS (EI): *m*/*z* (%) = 334 (73) $[M]^+$, 167 (100).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.78; H, 5.48; N, 8.38.

2-(Benzhydrylamino)benzonitrile (3r)[23]

By following the general procedure, **3r** was obtained.

Yield: 237 mg (83%); white solid; mp 97–112 °C.

IR (KBr): 3421 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.10 (s, 1 H), 5.60 (d, *J* = 4.1 Hz, 1 H), 6.50 (d, *J* = 8.6 Hz, 1 H), 6.68 (t, *J* = 15.2, 7.6 Hz, 1 H), 7.42 (dd, *J* = 7.8, 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.3, 96.3, 112.2, 117.1, 117.8, 127.3, 127.9, 129.0, 132.7, 134.1, 141.3, 149.1.

MS (EI): *m*/*z* = 284 $[M + H]^+$.

2-(Benzhydrylamino)-4-(trifluoromethyl)benzonitrile (3s)[12]

By following the general procedure, **3s** was obtained.

Yield: 268 mg (76%); white solid; mp 126–128 °C.

IR (KBr): 3407, 2220 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.33 (br d, *J* = 4.6 Hz, 1 H), 5.64 (d, *J* = 5.0 Hz, 1 H), 6.73 (s, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 7.29–7.39 (m, 10 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 8.76 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.4, 99.4, 108.9 (q, J_{CF} = 3.8 Hz), 113.6 (q, J_{CF} = 3.8 Hz), 116.7, 123.3 (q, J_{CF} = 273.2 Hz), 127.4, 128.3, 129.3, 133.6, 135.9 (q, J_{CF} = 32.6 Hz), 140.6, 149.3.

MS (FAB): *m*/*z* = 353 $[M + H]^+$.

1-[4-(Benzhydrylamino)phenyl]ethan-1-one (3t)[24]

By following the general procedure, **3t** was obtained.

Yield: 166 mg (55%); white powder; mp 139–141 °C.

IR (KBr): 3358, 1596 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 4.75 (br d, *J* = 3.9 Hz, 1 H), 5.61 (d, *J* = 4.6 Hz, 1 H), 6.53 (d, *J* = 8.9 Hz, 2 H), 7.26–7.37 (m, 10 H), 7.79 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 62.5, 112.5, 127.3, 127.5, 127.9, 129.1, 130.8, 141.9, 151.1, 196.5.

MS (FAB): *m*/*z* = 302 $[M + H]^+$.

Ethyl 4-(Benzhydrylamino)benzoate (3u)[25]

By following the general procedure, **3u** was obtained.

Yield: 272 mg (82%); white solid; mp 120–122 °C.

IR (KBr): 3349, 1686, 1602 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 4.66 (br s, 1 H), 5.59 (s, 1 H), 6.51 (d, *J* = 8.9 Hz, 2 H), 7.26–7.34 (m, 10 H), 7.81 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 60.3, 62.5, 112.5, 119.4, 127.6, 127.8, 129.0, 131.5, 142.1, 150.9, 166.9.

MS (FAB): *m*/*z* = 332 $[M + H]^+$.

Synthesis of 3v and 4

A mixture of 4-nitronaphthalen-1-amine **1b** (188 mg, 1 mmol), $NaAuCl_4 \cdot 2H_2O$ (20 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) (18 mg, 0.05 mmol) and benzhydrol **2a** (1.2 mmol) in H_2O (4 mL) was heated at 120 °C for 16 h under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give N-benzylated product **3v** (237 mg, 0.67 mmol) and C-benzylated product **4** (71 mg, 0.20 mmol).

N-Benzhydryl-4-nitronaphthalen-1-amine (3v)

Mp 198–200 °C; brown solid.

IR (KBr): 3437 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.69 (br d, *J* = 4.4 Hz, 1 H), 5.83 (d, *J* = 4.7 Hz, 1 H), 6.39 (d, *J* = 8.9 Hz, 1 H), 7.55 (ddd, *J* = 9.2, 6.2, 1.3 Hz, 1 H), 7.72 (ddd, *J* = 8.8, 5.7, 1.3 Hz, 1 H), 7.88 (d, *J* = 8.5 Hz, 1 H), 8.31 (d, *J* = 8.8 Hz, 1 H), 9.00 (dd, *J* = 8.8, 0.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.7, 103.6, 102.1, 122.0, 125.0, 126.0, 126.5, 127.4, 128.2, 128.5, 128.9, 129.2, 129.6, 135.8, 140.9, 148.0.

MS (EI): *m*/*z* = 354 $[M + H]^+$.

2-Benzhydryl-4-nitronaphthalen-1-amine (4)

Brown solid; mp 198–201 °C.

IR (KBr): 3377, 1641, 1558 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.89 (br s, 2 H), 5.59 (s, 1 H), 7.16 (dd, *J* = 6.9, 1.6 Hz, 4 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.70 (t, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 1 H), 7.96 (s, 1 H), 8.91 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 49.7, 119.2, 121.9, 124.0, 124.1, 125.9, 127.1, 127.2, 129.1, 129.7, 130.6, 130.9, 132.2, 142.6, 150.5.

MS (EI): *m*/*z* (%) = 354 (100) $[M]^+$.

HRMS-EI: *m*/*z* $[M^+]$ calcd for $C_{23}H_{18}N_2O_2$: 354.1368; found: 354.1367.

N-[Cyclopropyl(phenyl)methyl]-4-nitroaniline (3w)[20]

By following the general procedure, **3w** was obtained.

Yield: 181 mg (68%); yellow solid; mp 60–62 °C.

IR (KBr): 3411, 1598, 1513 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.39 (ddd, *J* = 9.6, 9.6, 5.3 Hz, 1 H), 0.48 (ddd, *J* = 9.4, 9.4, 4.8 Hz, 1 H), 0.57–0.71 (m, 2 H), 1.19–1.28 (m, 1 H), 3.84 (br d, *J* = 8.0 Hz, 1 H), 5.17 (br s, 1 H), 6.41 (d, *J* = 9.2 Hz, 2 H), 7.26–7.37 (m, 5 H), 7.97 (d, *J* = 9.4 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 3.4, 4.8, 18.4, 60.7, 111.4, 126.0, 126.4, 127.0, 128.4, 135.7, 142.8, 153.7.

MS (FAB): *m*/*z* = 269 $[M + H]^+$.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611519.

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