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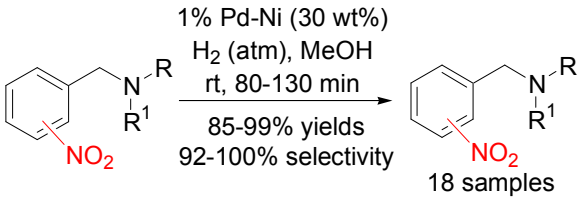
Graphical Abstract

Hydrogenation of (*N,N*-Disubstituted Aminomethyl) Nitrobenzenes to (*N,N*-Disubstituted Aminomethyl) Anilines Catalyzed by Palladium-Nickel Bimetallic Nanoparticles

Hailin Bao, Dingsheng Wang, Xinyan Wang,* Chuanjie Cheng, Yadong Li, Yuefei Hu*



A Pd-Ni bimetallic nanoparticles catalyzed hydrogenation of (*N,N*-disubstituted aminomethyl) nitrobenzenes to (*N,N*-disubstituted aminomethyl) anilines was achieved chemoselectively.

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ARTICLE TYPE

Hydrogenation of (*N,N*-Disubstituted Aminomethyl) Nitrobenzenes to (*N,N*-Disubstituted Aminomethyl) Anilines Catalyzed by Palladium-Nickel Bimetallic Nanoparticles

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Since palladium-catalysts have strong abilities for both hydrogenation of nitro-group and hydrogenolysis of benzylamine, they have a much lower chemoselectivity for the hydrogenation of (*N,N*-disubstituted aminomethyl) nitrobenzenes. In this article, the component stable Pd-Ni bimetallic nanoparticles were prepared by simply heating Raney-Ni and Na_2PdCl_4 together in water. They demonstrated novel synergistic effects when they were used as a bimetallic catalyst, by which a highly efficient and chemoselective hydrogenation of (*N,N*-disubstituted aminomethyl) nitrobenzenes to (*N,N*-disubstituted aminomethyl) anilines was achieved.

Introduction

The catalytic hydrogenation of nitrobenzenes is the most preferred method for the synthesis of anilines due to its high efficiency and easy procedures. Pd-catalysts are often employed for this purpose in both academic and industry laboratories because they have lower costs than Pt-catalysts and higher efficiency than Ni-catalysts.[1] Since Pd-catalysts also have a strong ability for the catalytic hydrogenolysis of carbon-heteroatom bonds, they have a much lower chemoselectivity for the hydrogenation of (*N,N*-disubstituted aminomethyl) nitrobenzenes **1**.[2,3]

In 1999, the first small-molecule, non-peptide CCR5 antagonist TAK-779 was reported to have highly potent and selective anti-HIV-1 activity.[4] As shown in Figure 1, its molecule contains a structural unit of (*N,N*-disubstituted aminomethyl) aniline **2**. In recent years, the syntheses of structural units **2** have been gaining importance because they have been recognized as key pharmacophores and synthetic intermediates in drug discovery.[5-7] The most convenient synthesis of **2** can be achieved by chemoselective reduction of **1**. Unfortunately, the most reliable method for this conversion was the dissolving metal reduction[5] rather than the catalytic hydrogenation.[7]

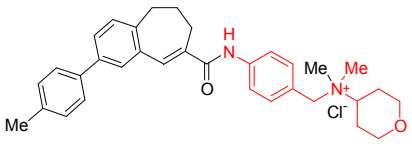
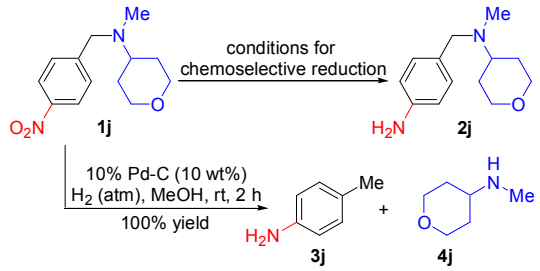


Figure 1. The structure of TAK-779.

As shown in Scheme 1, a detailed study was reported by Hashimoto et al[5f] for the synthesis of *N*-[(4-aminophenyl)-methyl]tetrahydro-*N*-methyl-2*H*-pyran-4-amine (**2j**) from *N*-[(4-nitrophenyl)methyl]tetrahydro-*N*-methyl-2*H*-pyran-4-amine (**1j**). Under the catalytic hydrogenation conditions, the desired product **2j** was obtained in trace yield over Pd-C or Raney-Ni catalyst (entries 1 and 2). Finally, the combination of $SnCl_2$/aq. HCl was employed as a reducing reagent for this conversion. The experiment in entry 1 was carefully repeated in our laboratory and the benzyl-nitrogen bond in **1j** was hydrogenolyzed completely to give the corresponding **3j** and **4j**.



entry	reducing reagent	yield of **2j** (%)
1	Pd-C/H_2	trace
2	Raney-Ni/H_2	trace
3	Sn/aq. HCl	98.8
4	$SnCl_2$/aq. HCl	99.5

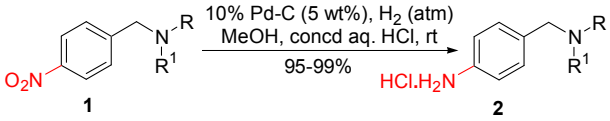
Scheme 1. A detailed study for the reduction of **1j** to **2j**.

Herein, we would like to report a convenient preparation of Pd-Ni bimetallic nanoparticles. When they were used as a bimetallic catalyst, a general method was developed for highly efficient and chemoselective hydrogenation of **1** to **2**.

Results and Discussion

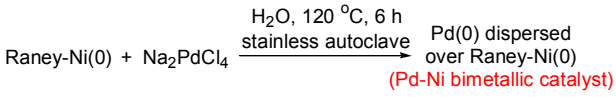
Traditionally, the chemoselectivity of Pd-catalysts are modulated by using the catalyst poisons. For example, PbO/$PbAc_2$ or

quinoline is employed for such purpose in Lindlar catalysts.[8] Rosenmund reduction can be well modulated by *in situ* adding thioquinanthrene or thiourea into the hydrogenation processes.[9] Pd-C(en) is a versatile catalyst for chemoselective hydrogenations, in which ethylenediamine is used as the poison.[10] However, these reported catalytic systems are not all suitable for the chemoselective hydrogenation of **1** to **2**. As shown in Scheme 2, this conversion was first achieved in our previous work,[11] but the concentrated aqueous HCl was used as the poison for the Pd-C catalyst.



Scheme 2. A reported chemoselective hydrogenation of **1** to **2**.

Recently, the catalytic applications of bimetallic nanoparticles have been developing quickly.[12] These bimetallic catalysts often showed novel catalytic activity and chemoselectivity based on their unique electronic effect (or ligand effect) and geometric effect (or strain effect). Many methods have been reported for the preparation of bimetallic catalysts in literature. However, our attention was attracted by several early reported references,[13] in which the bimetallic catalysts were prepared by simply mixing a Raney-metal [M = Ni(0), Cu(0)] with a noble metal precursor [M^1 = Pt(IV) Ru(III), Au(III), Pd(II)] together. Since the Raney-metal is a porous solid and has low redox potential, the noble metal precursor is reduced to a zero-valent metal [M^1(0)] to disperse on the surface of the Raney-metal. In these preparations, Raney-metal plays three roles as a reducing reagent, a support and one component of the bimetallic catalyst. Thus, we were inspired to prepare a Pd-Ni bimetallic catalyst by the similar method. As shown in Scheme 3, when the mixture of Raney-Ni (99 wt%) and Na_2PdCl_4 (containing 1 wt% of Pd) in water was heated at 120 °C for 6 h in an autoclave, a component stable Pd-Ni bimetallic catalyst was obtained as black powders.



Scheme 3. Preparation of the Pd-Ni bimetallic catalyst.

ICP analyses showed that Pd/Ni ratio in this bimetallic catalyst was about 1:99 ± 3 (by wt%). TEM images showed that the bimetallic catalyst was nanosized particles (Figure 2). Since it contains only 1 wt% of Pd(0), its XRD patterns had no significant differences with Raney-Ni (Figure 3) and the peak of only Pd(111) was observed.

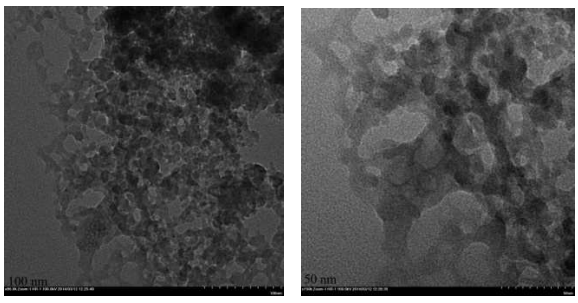


Figure 2. TME images of Pd-Ni bimetallic nanoparticles.

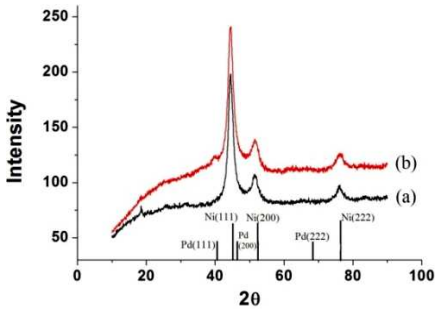
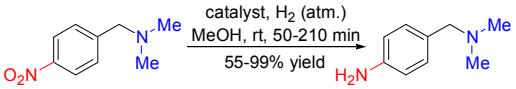


Figure 3. XRD patterns of Raney-Ni (a) and Pd-Ni bimetallic nanoparticles (b).

Then, the catalytic property of this Pd-Ni bimetallic catalyst was tested by using the hydrogenation of 4-(*N,N*-dimethyl-aminomethyl) nitrobenzene (**1a**) into 4-(*N,N*-dimethyl-aminomethyl) aniline (**2a**) as a model reaction. As shown in entry 1 in table 1, **2a** was obtained in 90% yield and 93% chemoselectivity over Pd-C catalyst. Low conversion of **1a** was observed over Raney-Ni and a mixture was obtained caused by the hydrogenation intermediates (entry 2).[14] As was expected, **1a** was hydrogenated into **2a** in quantitative yield and chemoselectivity over Pd-Ni bimetallic catalyst (entry 3). Since this experiment employed the same amounts of palladium (net weight) as that in entry 1 and nickel (net weight) as that in entry 2, the Pd-Ni bimetallic catalyst clearly demonstrated its advantages and synergistic effects. Use of 30 wt% of the Pd-Ni bimetallic catalyst gave the same excellent results (entry 4), while use of 20 wt% of the Pd-Ni bimetallic catalyst resulted in low conversion of **1a** (entry 5). However, this problem can be solved easily by slightly increasing the hydrogen pressure (entries 6 and 7).

Table 1. Hydrogenations of **1a** catalyzed by three catalysts[a]

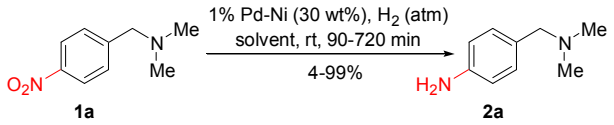


Entry	catalyst (wt%)	net weight of metal (mg)	time (min)	yield of **2a** (%)[b]	selectivity (%)
1	5% Pd-C (10)	Pd (0.9)	120	90	95
2	Raney-Ni (50)	Ni (90)	150	85[c]	mixture
3	1% Pd-Ni (50)	Pd (0.9) Ni (89.1)	50	99	100
4	1% Pd-Ni (30)	Pd (0.54) Ni (53.5)	90	99	100
5	1% Pd-Ni (20)	Pd (0.36) Ni (25.6)	140	85	100
6	1% Pd-Ni (10)	Pd (0.18) Ni (17.8)	180	55	100
7[d]	1% Pd-Ni (10)	Pd (0.09) Ni (8.91)	210	93	100

[a] A mixture of **1a** (180 mg, 1 mmol) and a catalyst in MeOH (10 mL) was stirred under H_2 at room temperature and atmospheric pressure (on an atmospheric pressure hydrogenation apparatus). [b] Separated yield was obtained. [c] 85% conversion of **1a** was obtained. [d] The hydrogenation proceeded under 50 psi.

Unlike the commercial Raney-Ni catalyst, Pd-Ni bimetallic catalyst (in both wet and dry forms) is stable to air and no auto-ignition has occurred so far. However, its catalytic activity was influenced significantly by the reaction solvents. As shown in table 2, all tested lower alcohols were excellent solvents for this catalytic hydrogenation (entries 1-4). But non-alcohol solvents, both polar solvents (entries 5-6) and non-polar solvents (entries 7-9), were not suitable for this purpose. This phenomenon may be partly caused by the fact that the Pd-Ni bimetallic nanoparticles could be fully dispersed in the lower alcohols, while it formed agglomerated particles in the non-alcohol solvents.

Table 2. Effect of the solvents on the hydrogenations of **1a**[a]

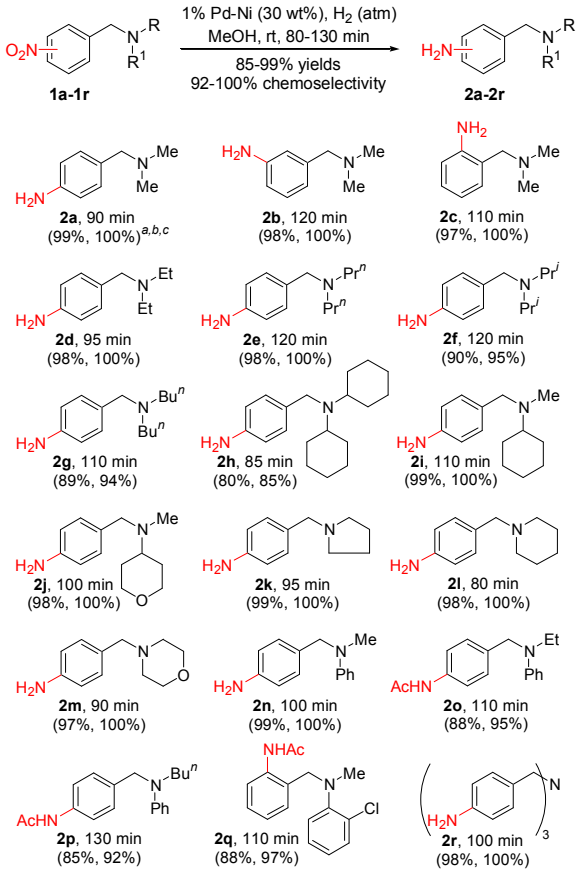


Entry	solvent	time (min)[b]	yield of **2a** (%)[c]
1	MeOH	90	99
2	EtOH	110	96
3	*i*-PrOH	210	94
4	*n*-BuOH	330	93
5	THF	600	81
6	EtOAc	720	75
7	DCM	480	47
8	cyclohexane	300	5
9	toluene	300	4

[a] A mixture of **1a** (180 mg, 1 mmol) and Pd-Ni bimetallic catalyst in the tested solvent (10 mL) was stirred under H_2 at room temperature and atmospheric pressure (on an atmospheric pressure hydrogenation apparatus). [b] The time was when the absorption of hydrogen ceased. [c] Separated yield was obtained.

Finally, the standard procedure was assigned as shown in Scheme 4 and the reaction scope was tested. There was no difference caused by the substituted position of a nitro-group on the benzene ring (**2a-2c**). But, the chemoselectivity was influenced significantly by the size of the group substituted on the benzylamine, and decreased sharply by the increase of the size (**2d-2h**, **2n-2p**). To improve the chemoselectivity of **2h**, the hydrogenation of **1h** at 0 °C was tested. Unfortunately, the chemoselectivity of **2h** increased 9% while the yield of **2h** decreased 7% because the hydrogenation of **1h** automatically stopped within 16 h. We interestingly observed that the excellent chemoselectivity could be achieved as long as one group is a methyl group (**2i-2j**, **2n**). The cyclic substituents seemed to be "small-sized groups" and gave both quantitative yields and chemoselectivity (**2k-2m**). For easy purification of the analytical samples, three products were converted into their amides derivatives (**2o-2q**). To our surprise, **2r** was prepared smoothly in the presence of 40 wt% of Pd-Ni bimetallic catalysts.

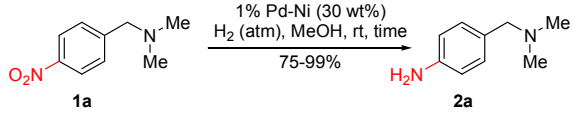
Since the Pd-Ni bimetallic catalyst has magnetic property, it can be separated and recovered conveniently in work-up process with a magnetic stirring bar, which could greatly facilitate the recycling of the catalyst. As shown in Table 3, a recycling study shows that the catalytic activity of the Pd-Ni bimetallic catalyst decreased steadily in the first three recycles (entries 1-3). But, the yield and chemoselectivity of the product **2a** were not influenced by prolonging the reaction time. Unfortunately, its catalytic activity dropped sharply in the fourth recycle (entry 4), presumably because of the loss of the "nonmagnetic palladium metal" during the separation and recovery of the catalyst. In fact, the proportion of palladium metal in the Pd-Ni bimetallic catalyst in the fourth recycle was 18% lower than that in the fresh catalyst.



[a] The numbers in the parathesis are the yield and the chemoselectivity, respectively. [b] Separated yield is obtained. [c] Chemoselectivity is determined by ^{1}H NMR spectra of the crude product.

Scheme 4. The scope of the chemoselective hydrogenation.

Table 3. Recycling study of the Pd-Ni bimetallic catalyst.[a]



recycle times	time (min)[b]	yield of **2a** (%)[c]
1	90	99
2	210	97
3	450	94
4	900	75[d]

[a] A mixture of **1a** (180 mg, 1 mmol) and Pd-Ni bimetallic catalyst in MeOH (10 mL) was stirred under H_2 at room temperature and atmospheric pressure (on an atmospheric pressure hydrogenation apparatus). [b] The time was when the absorption of hydrogen ceased. [c] Separated yield was obtained. [d] Only **1a** (25%) and **2a** (75%) were detected in the reaction mixture by ^{1}H NMR.

Conclusions

A highly efficient and chemoselective hydrogenation of (*N,N*-disubstituted aminomethyl) nitrobenzenes to (*N,N*-disubstituted aminomethyl) anilines was developed. Its success was due to the novel catalytic activity of the Pd-Ni bimetallic nanoparticles. In literature, the reported bimetallic catalyst usually demonstrated higher catalytic activity than both componential metals by their synergistic effects. However, our Pd-Ni bimetallic catalyst demonstrated that the catalytic activity of Raney-Ni was enhanced and the chemoselectivity of Pd was enhanced. This hydrogenation may be widely used since the Pd-Ni bimetallic catalyst can be prepared conveniently and the products are very useful in the drug discovery.

Experimental Section

General information

All melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets on a Nicolet FT-IR 5DX spectrometer. All spectra of ^{1}H NMR and ^{13}C NMR were recorded on a JEOL JNM-ECA 300 or 400 spectrometers in $CDCl_3$ and TMS was used as an internal reference. HRMS were obtained on a Bruker micrOTOF-Q II spectrometer.

Preparation of 1% Pd-Ni Bimetallic Catalyst. The suspension of Raney-Ni (1.0 g) and Na_2PdCl_4 (80.66 mg, containing 10 mg of palladium) in H_2O (8 mL) in a stainless teflon-lined 10-mL-capacity autoclave was heated at 120 ^oC for 6 h. After the reaction system was cooled down to room temperature, the black powders were collected and washed by water in three times. It was stored in distillated H_2O before uses.

Typical Procedure for Hydrogenation of 4-(*N,N*-Dimethyl-Aminomethyl) Nitrobenzene (1a) into 4-(*N,N*-Dimethyl-aminomethyl) Aniline (2a). A mixture of **1a** (180 mg, 1 mmol) and 1% Pd-Ni bimetallic catalyst (54 mg, 30 wt%) in MeOH (10 mL) was stirred under H_2 at room temperature and atmospheric pressure (on an atmospheric pressure hydrogenation apparatus) until the absorption of hydrogen ceased (90 min). After the catalyst was removed off by a magnetic stirring bar, the solution was evaporated in a vaporator to give the product **2a** as yellowish oil (148 mg, 99%), which is pure enough for ^{1}H and ^{13}C NMR determinations.[15a] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (d, 2H, J = 8.28 Hz), 6.64 (d, 2H, J = 7.76 Hz), 3.59 (s, 2H), 3.32 (s, 2H), 2.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.4, 130.3 (2C), 128.5, 114.9 (2C), 63.8, 45.0 (2C).

The similar procedure was used for the chemoselective hydrogenation of **1b–1r** to **2b–2r**. In some cases, the flash chromatography was required for the purification of the products.

3-(*N,N*-Dimethyl-aminomethyl) aniline (2b).[15b] Yellowish oil, 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11–7.09 (m, 1H), 6.69–6.57 (m, 3H), 3.62 (s, 2H), 3.33 (s, 2H), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.4, 140.2, 129.1, 119.4, 115.6, 113.9, 64.4, 45.4 (2C).

2-(*N,N*-Dimethyl-aminomethyl) aniline (2c).[15c] Yellowish oil, 97% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08–6.96 (m, 2H), 6.66–6.62 (m, 2H), 3.40 (s, 2H), 2.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.0, 130.3, 128.2, 123.3, 117.5, 115.4, 63.4, 44.9 (2C).

4-(*N,N*-Diethyl-aminomethyl) aniline (2d). Yellowish oil, 98% yield. IR (KBr) ν 3449, 2969, 2801, 1620, 1616, 1281 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, 2H, J = 8.24 Hz), 6.63 (d, 2H, J = 8.72 Hz), 3.59 (s, 2H), 3.46 (s, 2H), 2.50 (q, 4H, J = 7.36 Hz), 1.03 (t, 6H, J = 7.32 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 130.1 (2C), 129.5, 114.9 (2C), 56.8, 46.4 (2C), 11.6 (2C); HRMS (ESI-TOF) (*m/z*): calcd for $C_{11}H_{18}N_2$, $[M+H]^+$ 179.1543; found 179.1545.

4-(*N,N*-Dipropyl-aminomethyl) aniline (2e). Yellowish oil, 98% yield. IR (KBr) ν 3349, 2798, 1621, 1516, 1459, 1274, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10 (d, 2H, J = 11.0 Hz), 6.64 (d, 2H, J = 11.4 Hz), 3.55 (s, 2H), 3.43 (s, 2H), 2.34 (t, 4H, J = 10.08 Hz), 1.49–1.42 (m, 4H), 0.84 (t, 6H, J = 10.08 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 130.0 (2C), 129.8, 114.8 (2C), 57.9, 55.6 (2C), 20.1 (2C), 11.9 (2C); HRMS (ESI-TOF) (*m/z*): calcd for $C_{13}H_{22}N_2$, $[M+H]^+$ 207.1856; found 207.1857.

4-(*N,N*-Diisopyl-aminomethyl) aniline (2f). Yellowish oil, 90% yield. IR (KBr) ν 3353.12, 2964, 2811, 1620, 1514, 1462, 1272 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, 2H, J = 8.25 Hz), 6.63 (d, 2H, J = 8.58 Hz), 3.52 (s, 4H), 3.02–2.97 (m, 2H), 1.01 (S, 6H), 0.99 (S, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.5, 133.0, 128.9 (2C), 114.9 (2C), 48.1, 47.3 (2C), 20.7 (4C); HRMS (ESI-TOF) (*m/z*): calcd for $C_{13}H_{22}N_2$, $[M+H]^+$ 207.1856; found 207.1860.

4-(*N,N*-Dibutyl-aminomethyl) aniline (2g). Yellowish oil, 89% yield. IR (KBr) ν 3355, 2956, 2796, 1621, 1515, 1274 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, 2H, J = 8.28 Hz), 6.63 (d, 2H, J = 8.28 Hz), 3.58 (s, 2H), 3.44 (s, 2H), 2.37 (t, 4H, J = 7.32 Hz), 1.43–1.41 (m, 4H), 1.30–1.26 (m, 4H), 0.87 (t, 6H, J = 7.32 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9, 129.9 (2C), 129.8, 114.9 (2C), 57.9, 53.2 (2C), 29.1 (2C), 20.6 (2C), 14.1 (2C); HRMS (ESI-TOF) (*m/z*): calcd for $C_{15}H_{26}N_2$, $[M+H]^+$ 235.2169; found 235.2165.

4-(*N,N*-Dicyclohexyl-aminomethyl) aniline (2h).[11] Yellowish oil, 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (d, 2H, J = 11.0 Hz), 6.62 (d, 2H, J = 10. 6 Hz), 3.62 (s, 2H), 3.54 (s, 2H), 2.54–2.49 (m, 2H), 1.73–1.15 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.3, 133.5, 128.7 (2C), 114.9 (2C), 57.4 (2C), 49.3, 31.9 (4C), 26.5 (4C), 26.3 (2C).

4-(*N*-Methyl-*N*-cyclohexyl-aminomethyl) aniline (2i).[5e] Yellowish oil, 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, 2H, J = 8.25 Hz), 6.64 (d, 2H, J = 8.24 Hz), 3.57 (s, 2H), 3.44 (s, 2H), 2.44–2.39 (m, 1H), 2.16 (s, 3H), 1.85–1.16 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9, 130.0, 129.8 (2C), 114.9 (2C), 62.1, 57.2, 37.4, 28.6 (2C), 26.4, 26.0 (2C).

4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)-aminomethyl] aniline (2j).[5f] Yellowish oil, 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, 2H, J = 7.76 Hz), 6.64 (d, 2H, J = 8.24 Hz), 4.00–4.03 (m, 2H), 3.49 (s, 2H), 3.39 (s, 2H), 3.38–3.35 (m, 2H),

2.65–2.63 (m, 1H), 2.20 (s, 3H), 1.75–1.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.3, 130.0 (2C), 129.0, 115.0 (2C), 67.6 (2C), 59.3, 57.2, 37.2, 29.1 (2C).

4-(Pyrrolidin-1-yl)methyl aniline (2k). Yellowish oil, 99% yield. IR (KBr) ν 3372, 2929, 1623, 1582, 1382, 1288 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (d, 2H, J = 8.24 Hz), 6.64 (d, 2H, J = 8.24 Hz), 3.60 (s, 2H), 3.50 (s, 2H), 2.49–2.46 (m, 4H), 1.78–1.75 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 130.1 (2C), 129.3, 114.9 (2C), 60.1, 53.9 (2C), 23.3 (2C); HRMS (ESI-TOF) (*m/z*): calcd for $C_{11}H_{16}N_2$, $[M+H]^+$ 177.1386; found 177.1388.

4-(Piperidin-1-yl)methyl aniline (2l).[5d] Yellowish oil, 98% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, 2H, J = 8.28 Hz), 6.63 (d, 2H, J = 8.24 Hz), 3.60 (s, 2H), 3.38 (s, 2H), 2.42–2.30 (m, 4H), 1.61–1.52 (m, 4H), 1.42–1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 130.4 (2C), 128.1, 114.8 (2C), 63.3, 54.2 (2C), 25.9 (2C), 24.4.

4-(Morpholin-1-yl)methyl aniline (2m). Yellowish solid, mp 100–102 °C (lit.[15d] mp 100–102 °C), 97% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 2H, J = 8.24 Hz), 6.64 (d, 2H, J = 8.25 Hz), 3.70–3.67 (m, 4H), 3.62 (s, 2H), 3.37 (s, 2H), 2.42–2.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.4, 130.3 (2C), 127.5, 114.9 (2C), 67.0 (2C), 63.0, 53.5 (2C).

4-(*N*-Methyl-*N*-phenyl-aminomethyl) aniline (2n).[15e] Yellowish oil, 99% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21–7.19 (m, 2H), 6.75–6.58 (m, 7H), 4.38 (s, 2H), 3.55 (s, 2H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.9, 145.1, 129.0 (2C), 128.6, 127.9 (2C), 116.3, 115.2 (2C), 112.4 (2C), 56.0, 38.1.

***N*-[4-(*N*-Ethyl-*N*-phenyl-aminomethyl)phenyl] acetamide (2o).** Yellowish oil, 88% yield. IR (KBr) ν 3285, 3185, 2967, 1658, 1598, 1505, 1408, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.14 (m, 7H), 6.69–6.63 (m, 3H), 4.46 (s, 2H), 3.44 (q, 2H, J = 6.87 Hz), 2.14 (s, 3H), 1.18 (t, 3H, J = 6.87 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 148.3, 136.5, 135.1, 129.1 (2C), 127.0 (2C), 120.2 (2C), 116.0, 112.1 (2C), 53.4, 45.0, 24.3, 12.0; HRMS (ESI-TOF) (*m/z*): calcd for $C_{17}H_{20}N_2O$, $[M+Na]^+$: 291.1468; found 291.1463.

***N*-[4-(*N*-Butyl-*N*-phenyl-aminomethyl)phenyl] acetamide (2p).** Yellowish oil, 85% yield. IR (KBr) ν 3286, 2952, 2867, 1659, 1599, 1505, 1408, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.13 (m, 7H), 6.67–6.63 (m, 2H), 4.48 (s, 2H), 3.33–3.38 (m, 2H), 2.15 (s, 3H), 1.62–1.60 (m, 2H), 1.35–1.33 (m, 2H), 0.94 (t, 3H, J = 9.64 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.3, 148.5, 136.4, 135.1, 129.1 (2C), 127.0 (2C), 120.2 (2C), 115.9, 112.1 (2C), 54.0, 51.0, 29.2, 24.4, 20.3, 13.9; HRMS (ESI-TOF) (*m/z*): calcd for $C_{19}H_{24}N_2O$, $[M+Na]^+$ 319.1781; found 319.1779.

***N*-[2-[*N*-Methyl-*N*-(2-chlorophenyl)-aminomethyl]phenyl] acetamide (2q).** Yellowish oil, 88% yield. IR (KBr) ν 3260, 2854, 2803, 1686, 1516, 1443, 1304 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.82 (s, 1H), 8.22–8.19 (m, 1H), 7.40–7.02 (m, 7H), 4.17 (s, 2H), 2.62 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 148.4, 138.3, 130.5, 130.2, 129.5, 128.6, 127.8, 125.3, 125.2, 123.4, 121.9, 121.6, 58.8, 41.9, 24.7; HRMS (ESI-TOF) (*m/z*): calcd for $C_{16}H_{17}ClN_2O$, $[M+Na]^+$ 311.0922; found 311.0920.

Tris-(4-aminobenzyl)-amine (2r).[15f] Yellow gum, 98% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, 6H, J = 8.25 Hz), 6.66 (d, 6H, J = 8.25 Hz), 3.66 (s, 6H), 3.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.1 (3C), 130.4 (3C), 129.2 (6C), 115.0 (6C), 52.5 (3C).

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Notes and references

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† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra for products **2a**-**2r**. See DOI: 10.1039/b000000x/

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3 In general, the order of ease of hydrogenolysis of benzylamines is tertiary > secondary > primary. *N,N*-Disubstituted benzylamine smoothly underwent a hydrogenolysis over Pd-C catalyst, while benzylamine and *N*-monosubstituted benzylamine usually stayed intact. Therefore, only *N,N*-disubstituted benzylamines were suitable to be used as protective groups, see: T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn., John Wiley & Sons, Inc., New York, 1999.

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