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Direct conversion of phenols into primary anilines with hydrazine catalyzed by palladium†

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Primary anilines are essential building blocks to synthesize various pharmaceuticals, agrochemicals, pigments, electronic materials, and others. To date, the syntheses of primary anilines mostly rely on the reduction of nitroarenes or the transition-metal-catalyzed Ullmann, Buchwald–Hartwig and Chan–Lam cross-coupling reactions with ammonia, in which non-renewable petroleum-based chemicals are typically used as feedstocks via multiple step syntheses. A long-standing scientific challenge is to synthesize various primary anilines directly from renewable sources. Herein, we report a general method to directly convert a broad range of phenols into the corresponding primary anilines with the cheap and widely available hydrazine as both amine and hydride sources with simple Pd/C as the catalyst.

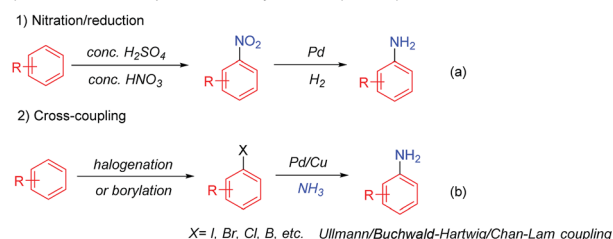
Primary anilines, as the parent molecules of aromatic amines, are vital and well exploited building blocks towards a wide range of pharmaceuticals, agrochemicals, plastics, electronic materials, dyes and resins.¹ Due to their importance, various methods have been explored to synthesize primary anilines. The nitro-reduction or the Ullmann, Buchwald–Hartwig and Chan–Lam cross-coupling reactions represent the very successful methods to build primary anilines nowadays. However, in most cases, such methods rely on the starting materials derived from non-renewable petroleum based chemicals (BTX, benzene, toluene, xylenes *etc.*),² in which extra pre-functionalization steps of arenes by nitration,³ halogenation⁴ and borylation⁵ are required to generate the corresponding aromatic nitro compounds, arylhalides and arylboron compounds in order to form primary anilines (Scheme 1a and b).⁶ On the other hand, naturally abundant phenols, which constitute some of the main units of lignin bio-mass and are widely obtainable at very low cost from coal and cumene industrial processes, are often considered as the alternative renewable aromatic feedstocks.⁷ Because of their sustainable feature, it is highly desirable to develop a method to directly convert phenols into primary anilines.

To this end, only gas-phase direct amination of phenol into aniline was successful, however, under very harsh conditions, in which phenol was vaporized to gas and then reacted with a large excess amount of ammonia and hydrogen gases at very high temperature (>250 °C).^{7d,8} Recently, a liquid phase phenol to aniline transformation was reported, but still requiring high

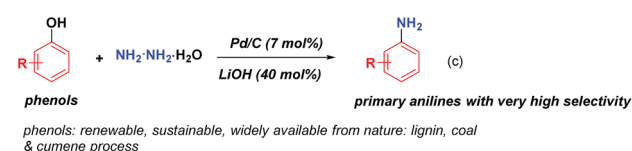
temperature (200 °C) and large excess amounts of ammonia gas and hydrogen gas with a very limited substrate scope (phenol and *o/m/p*-cresols); and at relatively lower temperature, this transformation suffered from both low conversion of phenol and poor selectivity towards the primary aniline, which can be attributed to the weak nucleophilicity of ammonia and the low stability of the cyclohexylimine intermediate. Such an intermediate is prone to undergo a reduction process to form cyclohexylamine under reductive conditions.⁹ Therefore, a general and relatively mild phenol to primary aniline transformation is yet to be developed.

Hydrazine, as the simplest diamine, is an inexpensive, widely available and easy-to-handle amine source.¹⁰ It possesses stronger nucleophilicity than ammonia due to the α -effect of the hydrazine nitrogen atom;¹¹ moreover, the corresponding cyclohexanone hydrazone is isolatable and more stable than

A) From non-renewable petroleum industry aromatics (BTX *etc.*):



B) From renewable aromatics (phenols) - directly convert phenols to primary anilines (this work):



Scheme 1 Primary aniline synthesis.

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cyclohexylimine.¹² Previously, our group utilized hydrazine as the amine source to couple with phenols to generate various *N*-cyclohexylanilines, in which the acid protonated the formation of cyclohexanone hydrazone intermediate and facilitated its reduction to the cyclohexylamines.¹³ With our previous successes to couple phenols with various substituted amines¹⁴ and hydrazine to produce *N*-substituted anilines,^{13,14} we contemplated the possibility of switching the phenol-hydrazine coupling selectivity towards primary anilines instead. We hypothesized that under less acidic or even basic conditions, the initial reduction of the cyclohexanone hydrazone intermediate might be slowed down. Instead, such a stable hydrazone intermediate could undergo the dehydrogenation process to rearomatize to phenylhydrazine with the catalysis of Pd/C, and then upon the reductive cleavage of the N-N bond of the phenylhydrazine intermediate, the primary aniline could be generated in a highly selective fashion (Scheme 1c).

To examine the feasibility of our hypothesis, we initially tested the reaction using phenol with 1.5 equiv. hydrazine monohydrate, 10 mol% Pd/C as the catalyst, and 50 mol% NaBH₄ as the hydride source in 1,4-dioxane (0.2 M) at 150 °C for 12 h (Table 1, entry 1). To our delight, the desired primary aniline **3a** could be obtained in 10% yield; however, the selectivity was poor with 46% *N*-cyclohexylaniline (**4**) as the main product along with 16% dicyclohexylamine, 1% *N*-phenylaniline (**5**), some cyclohexane and benzene. We attributed the poor selectivity to the water molecule in the hydrazine monohydrate

reagent, playing the role of a weak Brønsted acid to facilitate the reduction of the cyclohexanone hydrazone intermediate to generate cyclohexylamine, as our group discovered previously.¹³ To remove the water, various molecular sieves were investigated (Table S1†) and among them, the 4 Å molecular sieves showed the best efficiency, increasing the yield of the primary aniline **3a** to 58% (Table 1, entry 2). The solvent had a significant effect on this transformation (Table S2†): for example, switching the solvent from 1,4-dioxane to toluene decreased the primary aniline **3a** yield to 43% along with a lower conversion of phenol (Table 1, entry 3). Various catalysts were then examined (Table S3†) and the Pd/C (5 wt%) catalyst showed the best selectivity and highest yield of primary aniline **3a** among Pd/C (10 wt%), Pd/Al₂O₃ (5 wt%) and Ru/C (5 wt%).

To help the tautomerization process of the cyclohexanone hydrazone intermediate,¹⁵ catalytic amounts of Brønsted and Lewis acids were tested (Table S4†), however, leading to a decreased yield of primary aniline **3a** with an increased yield of *N*-cyclohexylaniline (**4**) (Table 1, entries 4 and 5). Conversely, with the basic additives (Table S5†), the yield of primary aniline **3a** remained almost unchanged (Table 1, entries 6 and 7). To increase the selectivity of primary aniline **3a** over *N*-cyclohexylaniline (**4**), a gentler hydride donor might be needed, since a stronger hydride donor would favor the reduction of the cyclohexanone hydrazone intermediate towards the undesired cyclohexylamine intermediate. Hydrazine, on the other hand,

Table 1 Optimization of the reaction conditions^a

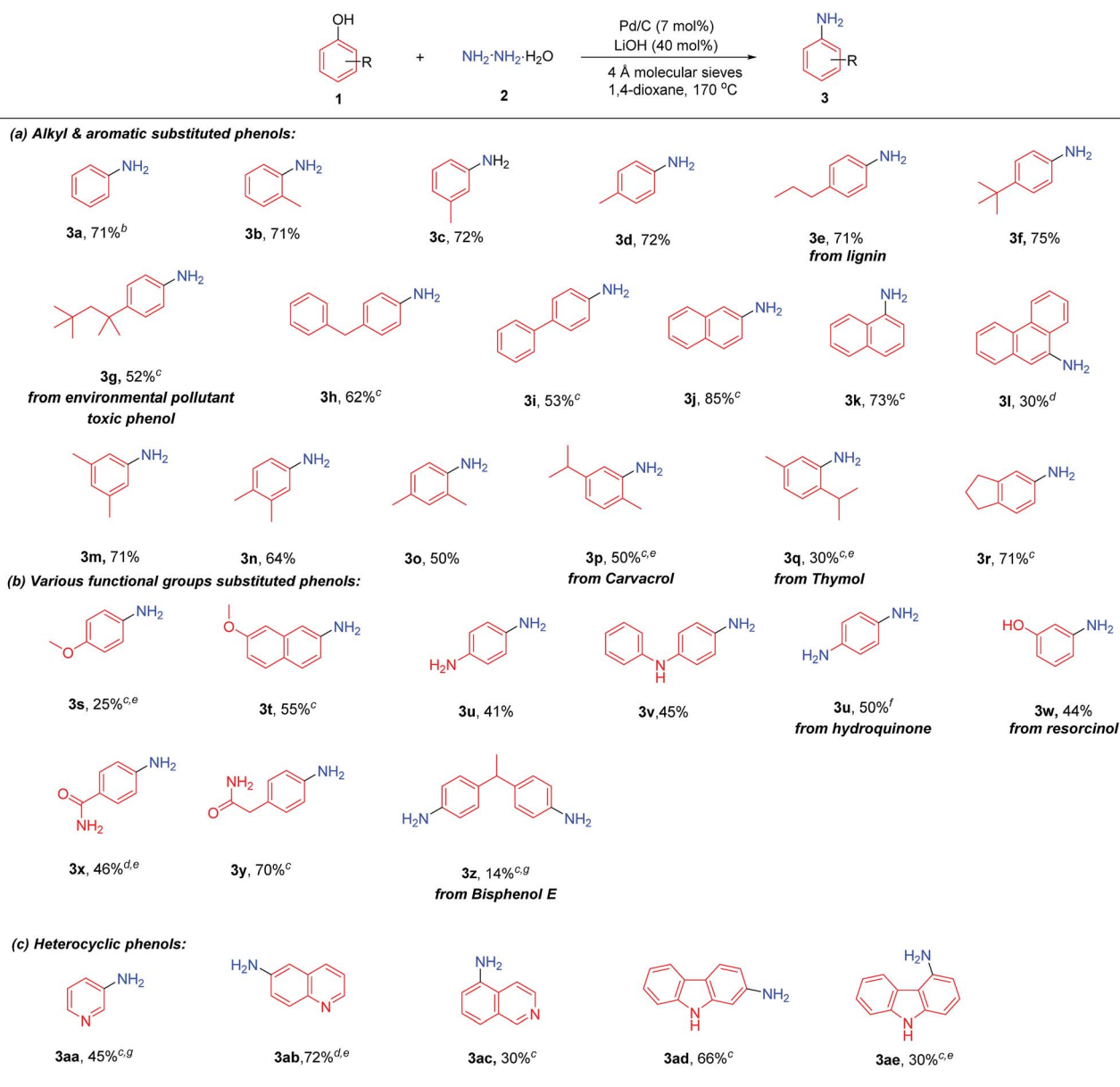
Entry	Hydride source (x mol%)	Additive (y mol%)	Conv. (%)	3a	Yield (%) 4	5
1 ^b	NaBH ₄ (50)	—	100	10	46	1
2	NaBH ₄ (50)	—	100	58	8	2
3 ^c	NaBH ₄ (50)	—	81	43	8	1<
4	NaBH ₄ (50)	ZnF ₂ (10)	100	30	36	11
5	NaBH ₄ (50)	HOAc (10)	81	41	12	3
6	NaBH ₄ (50)	Na ₂ CO ₃ (10)	100	55	16	4
7	NaBH ₄ (50)	NaO ^t Bu (10)	100	59	6	1
8	—	—	67	25	4	10
9 ^j	—	—	78	51	2	2
10 ^k	—	—	82	49	2	2
11 ^e	HCO ₂ Na (1.0)	—	100	64	3	1<
12 ^e	HCO ₂ Na (1.0)	LiOH (40)	100	68	2	1<
13 ^f	HCO ₂ Na (1.0)	LiOH (40)	100	69	4	2
14 ^{f,g,h}	HCO ₂ Na (1.0)	LiOH (40)	100	72	4	2
15 ^{d,g,h,i}	—	LiOH (40)	100	72 (71) ^l	<1	<1

^a Reaction conditions: phenol (0.2 mmol, 1 equiv.), N₂H₄·H₂O (0.3 mmol, 1.5 equiv.), 10 mol% of 5 wt% Pd/C, various hydride sources, and additives with 4 Å molecular sieves (100 mg per 0.3 mmol hydrazine) in 1,4-dioxane (0.2 M) were stirred under argon for 12 h; starting material conversions and NMR yields were given with 1,3,5-trimethoxybenzene as the internal standard, and yields were calculated based on phenol.

^b No molecular sieves were added. ^c Toluene was used as the solvent instead of 1,4-dioxane. ^d 3.0 equiv. $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ was used. ^e 3.0 equiv. N_2H_4 in THF solution (1 M) was used. ^f 2.25 equiv. N_2H_4 in THF solution (1 M) was used. ^g Reaction was run at 170 °C. ^h 7 mol% Pd/C was used.

ⁱ 0.4 mmol phenol was used. ^j 4.5 equiv. $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ was used. ^k 6.0 equiv. $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ was used. ^l Isolated yield. For details of optimization (Tables S1–S12), please see the ESI; HOAc = acetic acid.

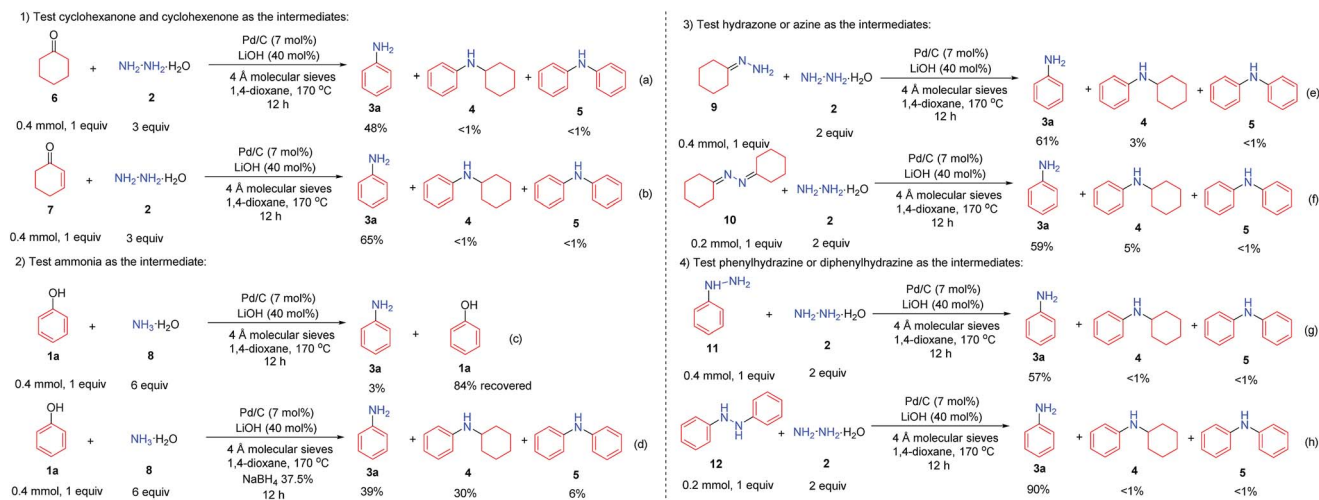
To increase the conversion of phenol, small amounts of various hydride donors were added (Table S8,[†] entries 5–9) and finally by using the relatively weak hydride donor HCO₂Na and with 3 equiv. of hydrazine in THF (1 M), the yield of primary aniline **3a** could be slightly increased to 64% (Table 1, entry 11 vs. 2). When LiOH was added to the reaction system, the desired primary aniline **3a** yield could be slightly increased to 68% (Table 1, entry 12),¹⁰ and decreasing the hydrazine amount from 3.0 equiv. to 2.25 equiv. maintained the same efficiency, generating the primary aniline **3a** in 69% yield (Table 1, entry

Table 2 Substrate scope of phenols^a

^a Reaction conditions: phenols (0.4 mmol, 1 equiv.), N₂H₄·H₂O (1.8 mmol, 4.5 equiv.), 7 mol% of 5 wt% Pd/C and 4 Å molecular sieves (100 mg per 0.3 mmol hydrazine) in 1,4-dioxane (0.2 M) were stirred under argon for 16 h; isolated yields were given. ^b 3 equiv. N₂H₄·H₂O was used and reaction was run for 12 h. ^c 37.5 mol% NaBH₄ was added. ^d 50 mol% NaBH₄ was added. ^e LiOH was not added. ^f 5 equiv. N₂H₄·H₂O was used. ^g 20 mol% of 5 wt% Pd/C was used.

To evaluate the synthetic potential of this direct conversion of phenols to primary anilines, several useful primary anilines applied in pharmaceuticals and organometallic chemistry were directly synthesized from the corresponding phenols (Scheme 2). Benzocaine (**3af**) (a pharmaceutical drug for oral ulcers and a local anesthetic), 4-aminopyridine (**3ag**)

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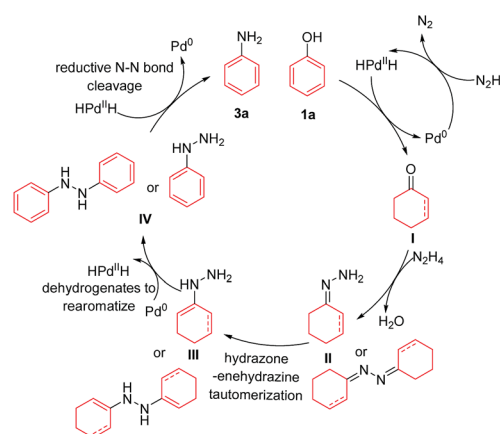
Scheme 3 Studies of reaction mechanism.

(used as a research agent to characterize potassium channels and a drug to manage multiple sclerosis¹⁷) and 5-aminoindole (3ah) (used as a key intermediate to prepare antimitotic and anticancer agents and HIV protease inhibitors¹⁸) could all be obtained in moderate to high yields directly from phenols (Scheme 2a–c). Moreover, protected tyrosine (amino acid) and tyramine (the decarboxylation product from tyrosine) were all suitable substrates for this reaction (3ai and 3aj) to afford the corresponding aniline analogues in one step (Scheme 2d and e). Besides, 8-aminoquinoline (3ak), which is widely used as a ligand and directing group in organometallic chemistry,¹⁹ was also produced efficiently in this transformation (Scheme 2f).

The plausible mechanism was investigated (Scheme 3). First, cyclohexanone (6) and cyclohexenone (7), as the two possible reduced forms of phenol, were reacted with hydrazine under the standard conditions, and both reactions afforded the desired primary aniline product 3a (in 48% and 65% yields, respectively) with excellent selectivity (Scheme 3a and b), indicating the possible involvement of both cyclohexanone (6) and cyclohexenone (7) as the reaction intermediates. Second, since hydrazine might decompose to ammonia under the current Pd/C catalyst system,¹⁰ ammonia was used as the amine source to react with phenol (1a) as the control experiments (Scheme 3c and d). Without additional hydride sources, phenol (1a) was mainly recovered in 84% yield (Scheme 3c), whereas in the presence of a small amount of NaBH₄, the primary aniline was generated in 39% yield but with poor selectivity (Scheme 3d), showing the unlikely involvement of ammonia as the intermediate. Third, the two possible intermediates hydrazone 9 and azine 10 were tested (Scheme 3e and f). Both of them could generate the primary aniline 3a with good yield and selectivity under standard conditions, demonstrating that they are possible intermediates in this transformation. Finally, the possible intermediates phenylhydrazine 11 and diphenylhydrazine 12 were

examined (Scheme 3g and h): in both cases, the desired primary aniline 3a could be obtained in good yield and very high selectivity, indicating that both would be the possible intermediates involved in this transformation.

Based on the above mechanistic studies and literature reports, a tentative mechanism for this direct phenol to primary aniline reaction is proposed in Scheme 4. Initially, HPd^{II}H (palladium hydride) species can be generated either by the decomposition of N₂H₄ under the Pd/C catalyst¹⁰ or by NaBH₄ reacting with Pd/C in the cases that NaBH₄ is added.^{14c,e} The palladium hydride then reduces the phenol (1a) to cyclohexanone or cyclohexenone intermediate I.^{14a,c} Then, intermediate I can condense with hydrazine to afford the hydrazone or azine intermediate II, which is followed by the hydrazone–enehydrazine tautomerization to generate intermediate III.¹⁵ Then intermediate III can readily undergo dehydrogenation and rearomatize to form the phenylhydrazine type intermediate IV, and meanwhile regenerate the HPd^{II}H species.^{14a,c,e} Finally, reductive N–N bond cleavage of IV²⁰ produces the desired



Scheme 4 Tentative mechanism.



primary aniline product **3a** and regenerates the Pd⁰ species at the same time.

Conclusions

In conclusion, we have developed a general method to directly convert a wide range of naturally abundant and renewable phenols into the corresponding primary anilines with the cheap and easy-to-handle hydrazine, acting as both amine and hydride sources, under relatively mild conditions with simple Pd/C as the catalyst. Bio-active phenols, such as carvacrol, thymol, hydroquinone, resorcinol, tyrosine and tyramine derivatives, are all appropriate substrates in this transformation and moreover, some useful primary anilines (shown in Scheme 2) could be directly synthesized by this protocol as well. Ongoing studies of other direct phenol amination methods are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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