

# Synthesis of Substituted Anilines from Cyclohexanones Using Pd/C–Ethylene System and Its Application to Indole Synthesis

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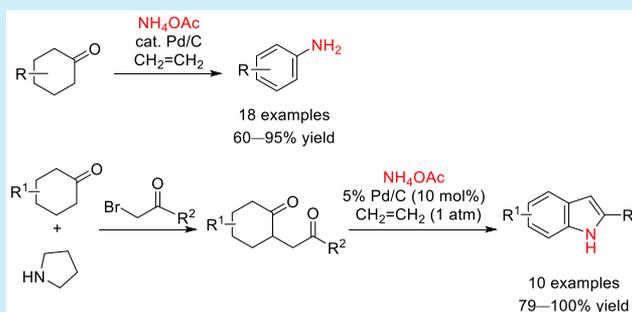


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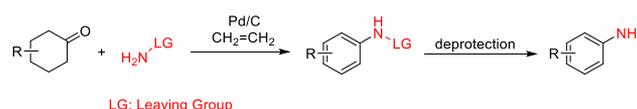
**ABSTRACT:** The synthesis of anilines and indoles from cyclohexanones using a Pd/C–ethylene system is reported. A simple combination of  $\text{NH}_4\text{OAc}$  and  $\text{K}_2\text{CO}_3$  under *nonaerobic* conditions was found to be the most suitable to perform this reaction. Hydrogen transfer between cyclohexanone and ethylene generates the desired products. The reaction tolerates a variety of substitutions on the starting cyclohexanones.



Anilines are one of the most fundamental chemicals used in industries.<sup>1</sup> Therefore, development of methods to synthesize anilines is one of the most important fields in both industry and academia. The existing methods for aniline synthesis are summarized in Scheme 1. Conventionally, anilines are synthesized by the nitration of benzene, followed by reduction with  $\text{Sn}/\text{HCl}$ .<sup>2</sup> Palladium-catalyzed coupling of aryl halides and ammonia as an extension of the Buchwald–Hartwig amination has also been reported. In 2006, Shen and Hartwig reported the palladium-catalyzed coupling of ammonia and lithium amide with aryl halides using the  $\text{Pd}(\text{II})\text{Cl}_2$ –Josiphos catalyst.<sup>3</sup> Following this, Buchwald and others reported the transition metal catalyzed monoarylation of ammonia.<sup>4–6</sup>

Serious limitations of the conventional and cross-coupling methods for aniline synthesis include the difficulty in

## Scheme 2. Two Step Synthesis of Anilines

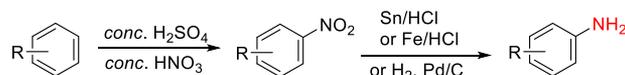


introducing substituents on the benzene ring, which is restricted by the *ortho/para*- and *meta*-orientation in electrophilic aromatic substitutions. Thus, it is often the case that several steps are required to prepare the starting material. Our strategy employs substituted cyclohexanones as the substrate, thereby allowing introduction of the substituents before aromatization.

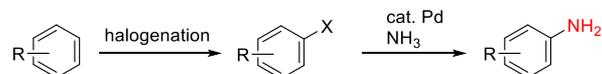
We previously report the synthesis of phenol from 2-cyclohexenol and 2-cyclohexenone using a Pd/C–ethylene system.<sup>7</sup> These reactions proceeded under *nonaerobic* conditions. Following our report on phenol synthesis in 2000, phenol synthesis from cyclohexanones and 2-cyclohexenone under *aerobic* conditions was reported. For example, Stahl and co-workers reported the  $\text{Pd}(\text{TFA})_2$ –2-dimethylaminopyridine-catalyzed *aerobic* dehydrogenation of cyclohexanone to phenol.<sup>8</sup> The use of molecular oxygen, namely, the reaction under *aerobic* conditions has advantage from the viewpoint of atom economy;<sup>9</sup> however, the reaction of concentrated

## Scheme 1. Previous Aniline Synthesis

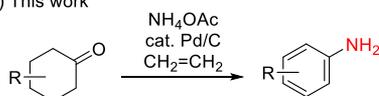
a) Conventional method (textbook method): nitration/reduction



b) Cross-coupling



c) This work



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Table 1. Reaction of Substituted Cyclohexanones with Ammonium Acetate<sup>a</sup>

Entry	Substrate	Product	Yield/% <sup>b,c</sup>	Entry	Substrate	Product	Yield/% <sup>b,c</sup>
1			86 <sup>d</sup> (73) <sup>d</sup>	10			80 (67)
2			27 <sup>d</sup> (71) <sup>d</sup>	11			95 <sup>e</sup> (87) <sup>f</sup>
3			78 <sup>d</sup> (69) <sup>d</sup>	12			84 (80)
4			78 <sup>d</sup> (63) <sup>d</sup>	13			74 (trace)
5			no reaction (63) <sup>d</sup>	14 <sup>g</sup>			63
6			67 <sup>d</sup> (71) <sup>d</sup>	15			63 <sup>h</sup> (89) <sup>h</sup>
7			75 (71)	16			56 (70)
8			65 (70)	17			70 <sup>e</sup> (75) <sup>f</sup>
9			39 (60)	18			(80) <sup>j</sup>

<sup>a</sup>All reactions were carried out in 0.5 mmol scale using 3 equiv of NH<sub>4</sub>OAc in the presence of 5% Pd/C (10 mol %) under ethylene atmosphere in CH<sub>3</sub>CN at 90 °C for 15 h unless otherwise noted. <sup>b</sup>The yields in the parentheses are those without K<sub>2</sub>CO<sub>3</sub>. <sup>c</sup>Isolated yield after silica-gel column chromatography unless otherwise noted. <sup>d</sup>GC analysis. <sup>e</sup>Reaction time: 5 h. <sup>f</sup>Reaction time: 3 h. <sup>g</sup>1,4-Dioxane was used instead of CH<sub>3</sub>CN; 110 °C, 21 h. <sup>h</sup>Reaction time: 48 h. <sup>i</sup>Using 5 equiv of NH<sub>4</sub>OAc was used (40 h). <sup>j</sup>4-Hydroxyindole was obtained in 11%.

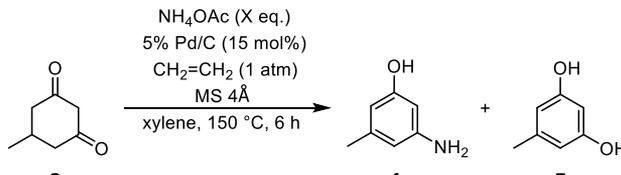
molecular oxygen is always in danger of explosion especially in industrial scale.

The reaction of *nonaerobic* condition is relatively safer than that of *aerobic* one. The synthesis of phenols<sup>10</sup> and resorcinols<sup>11</sup> using substituted cyclohexanones as substrates under *nonaerobic* conditions was a significant breakthrough. Although there are some reports on the palladium-catalyzed synthesis of arylamines under aerobic conditions,<sup>12</sup> those on the synthesis of arylamines under *nonaerobic* conditions are quite rare. In 2018, we reported a new synthetic method

involving the reaction of cyclohexanones with primary and secondary amines in the presence of the Pd/C under ethylene atmosphere to afford secondary and tertiary arylamines, respectively.<sup>13</sup> No reaction between cyclohexanone and ammonia occurred under the same conditions. At this stage, to synthesize primary amines, namely, anilines, from cyclohexanone requires two steps (Scheme 2). Therefore, a straightforward synthesis of anilines is expected.

In 2015, Li and co-workers also reported palladium-catalyzed synthesis of arylamines from phenol.<sup>14</sup> In 2019, Jin,

Table 2. Reaction of 5-Methyl-1,3-cyclohexanedione



entry	X/equiv	4/% <sup>a</sup>	5/% <sup>a</sup>
1	1.2	39	39
2	2	58	13
3	3	65	nd

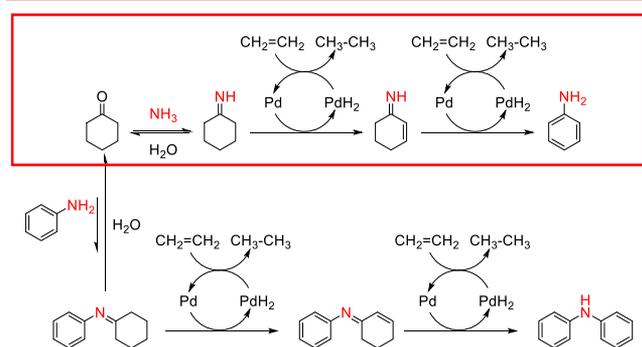
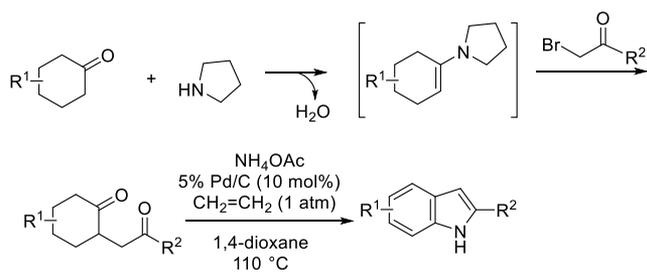
<sup>a</sup>Isolated yield. nd = not detected.

Figure 1. Plausible mechanism.

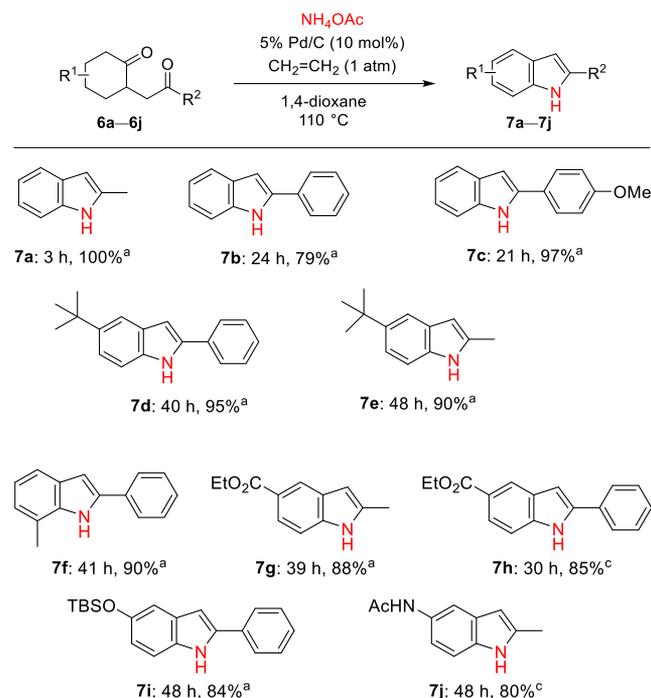
Scheme 3. Novel Synthetic Route to Substituted Indoles



Yamaguchi, and co-workers reported the synthesis of primary anilines from  $\text{NH}_3$  and cyclohexanones by utilizing preferential adsorption of styrene on the Pd nanoparticle surface.<sup>15</sup> Very recently, Leonori and co-workers reported aniline synthesis using photochemical system ( $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$  = photocatalyst,  $\text{Co}(\text{dmgH})_2(\text{DMAP})\text{Cl}$  = cobaloxime, under blue LEDs).<sup>16</sup> In this paper, we report the direct synthesis of anilines from cyclohexanones under *non-aerobic* conditions using the Pd/C–ethylene system. Furthermore, a new protocol for indole synthesis using the Pd/C–ethylene system is reported. Screening of various reaction conditions such as solvent (Table S1), nitrogen source, and additives (Table S2) suggested that ammonium acetate ( $\text{NH}_4\text{OAc}$ ) was the most suitable nitrogen source, while acetonitrile or 1,4-dioxane was the most suitable solvent. The effect of addition of potassium carbonate ( $\text{K}_2\text{CO}_3$ ) on the reactivity, namely, the yield of the products depended on the nature of the substrate.

The obtained results are summarized in Table 1. All reactions were carried out using 3 equiv of  $\text{NH}_4\text{OAc}$  in the presence of 5% Pd/C (10 mol %) under ethylene atmosphere in  $\text{CH}_3\text{CN}$ . The yields in the parentheses are those without  $\text{K}_2\text{CO}_3$ . The new method reported herein easily affords not

Table 3. Synthesis of Indoles

<sup>a</sup>Isolated yield after silica-gel column chromatography. <sup>b</sup>Isolated yield after recrystallization. <sup>c</sup>Using 15 mol % of 5% Pd/C.

only *ortho*-substituted (entries 2, 9, and 12, Table 1) and *para*-substituted (entries 4, 7, 8, 10, 11, 13, and 14) anilines but also *meta*-substituted (entry 3) and disubstituted (entries 5 and 6) anilines. Anilines having both electron-donating and -withdrawing groups were obtained in high yields. The present method is also effective for the synthesis of polycyclic benzenoid hydrocarbons (entries 15–18). When the yields of anilines were low, the starting material was not consumed even after raising the reaction temperature or increasing the amount of Pd/C. It should be mentioned that the addition of  $\text{K}_2\text{CO}_3$  was necessary for substrates bearing acid-labile functional groups. The addition of  $\text{K}_2\text{CO}_3$  decreased the reactivity when there is a substrate at  $\alpha$ -position (entries, 2, 5, and 9). From the above results, we assume the roles of  $\text{K}_2\text{CO}_3$  were to assist the enolization of ketones by deprotection of  $\alpha$ -hydrogen and easy generation of  $\text{NH}_3$  *in situ* which will lead to acceleration of the formation of imines. Thus, we were able to synthesize substituted aniline. Compared with the recently reported aniline synthesis using Pd nanoparticle or photochemical system ( $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]\text{PF}_6$ ,  $\text{Co}(\text{dmgH})_2(\text{DMAP})\text{Cl}$ , or LEDs), our method (Pd/C–ethylene) is apparently much simpler. It should be mentioned Pd/C was recycled and reused (Table S3).

Next, we examined the reaction of 5-methyl-1,3-cyclohexanedione with  $\text{NH}_4\text{OAc}$  in the presence of 5% Pd/C (15 mol %) under ethylene atmosphere. The use of three equivalent of  $\text{NH}_4\text{OAc}$  afforded 3-amino-5-methylphenol (4) in 65% yield (Table 2).

A plausible mechanism is shown in Figure 1. Cyclohexanone reacts with ammonia to generate an imine, which is followed by the first Pd/C-catalyzed hydrogen transfer with ethylene. The second hydrogen transfer affords aniline. The reaction of cyclohexanone with ammonia should be much faster than that with aniline. It is because of this that the formation of

diphenylamine was suppressed. Control experiments to support the proposed mechanism revealed that (1) ethylene behaved as a hydrogen acceptor, (2) cyclohexenone was not a key intermediate, and (3) phenol did not participate in the amination (Supporting Information).

The result in entry 18 of Table 1, inspired us to employ the Pd/C–ethylene system for the synthesis of indoles. Indoles are biologically important heteroaromatic moieties found in nature in compounds such as tryptophan and some alkaloids.<sup>17</sup> Indoles have been reported to exhibit antioxidant activity, anticonvulsant activity, and other biological activities. Many synthetic methods for indole derivatives have been reported so far. After the first indole synthesis by Baeyer in 1869,<sup>18</sup> more than 20 representative named reactions such as Fischer indole synthesis,<sup>19</sup> Reissert indole synthesis,<sup>20</sup> Madelung indole synthesis,<sup>21</sup> Nenitzescu indole synthesis,<sup>22</sup> Cadogan–Sundberg indole synthesis,<sup>23</sup> Hemetsberger indole synthesis,<sup>24</sup> Gassman indole synthesis,<sup>25</sup> Mori–Ban indole synthesis,<sup>26</sup> Sugawara indole synthesis,<sup>27</sup> Saegusa–Ito indole synthesis,<sup>28</sup> Leimgruber–Batcho indole synthesis,<sup>29</sup> Bartoli indole synthesis,<sup>30</sup> Larock indole synthesis,<sup>31</sup> and Fukuyama indole synthesis<sup>32</sup> have been developed. The starting materials in all these reactions, except the Nenitzescu indole synthesis,<sup>22</sup> are substituted benzenes, which are not always easy to prepare (the Supporting Information includes a list of the representative previous synthetic methods of indoles). In contrast to the reported methods, our method uses substituted cyclohexanones as the starting material. Scheme 3 shows the entire synthetic route from cyclohexanone to indole via 1,3-diketones.

As shown in Table 3, a variety of substituted indoles were synthesized in high and to excellent yield. In the case of indole synthesis, addition of K<sub>2</sub>CO<sub>3</sub> was not necessary. This may be because of the high reactivity for aromatization of intermediate enamine. Noteworthy is compound 7; only Bartoli indole synthesis<sup>28</sup> can introduce substituent at the 7 position so far. Our method has enables the introduction of substituents at any position of the indole by incorporating the substituents on the cyclohexanones, pyrrolidine, and  $\alpha$ -bromo ketones in advance. Therefore, providing a valuable approach to prepare functionalized indoles.

In conclusion, we have achieved the practical synthesis of anilines and indoles from cyclohexanones using a Pd/C–ethylene system under *nonaerobic* condition. The reaction proceeds in good yields and affords a new approach to the syntheses of these substrates which are important building blocks in industry and academia.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c04056>.

Solvent effect, effect of the nature of additives and their amounts, control experiments to support proposed mechanism, previous synthetic methods of indoles, general procedure for the synthesis of substituted anilines, general procedure for the synthesis of substituted indoles, characterization of products <sup>1</sup>H and <sup>13</sup>C NMR of products, references (PDF)

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### Notes

The authors declare no competing financial interest.

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