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Aromatization of Enamines Promoted by a Catalytic Amount of Pd/C. Synthesis of Aromatic Amines

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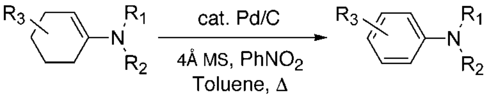
ABSTRACT



Aromatic amines were obtained efficiently from enamines by using a catalytic amount of Pd/C in the presence of nitrobenzene and 4 Å molecular sieves in refluxing toluene.

Aromatic amines are important synthetic intermediates that play a central role in many areas such as polymers,[1] photography,[2] and medicine.[3] Despite the simplicity of the arylamine structure, the synthesis of these compounds is often difficult. Procedures employing electrophilic aromatic substitution (S$_E$1 mechanism) that involve nitration followed by reduction[4] or direct amination[5] are incompatible with many functional groups and often require protection and deprotection steps. Aromatic amines can also be obtained by nucleophilic aromatic substitution under strongly basic conditions (S$_N$Ar,[6] benzyne,[7] or S$_{RN}$1[8] mechanisms). Arylalkylamines are typically prepared by reductive amination, which involves formation of an imine from an arylamine and subsequent reduction of the imine. However, this process requires an excess of the arylamine, and the reductions are sluggish.[9−12] Starting in 1983, palladium-catalyzed amination of aromatic halides has become the most prevalent method for arylamine synthesis.[13] Aromatic triflates can also be aminated by this process.[13a] Recently, it has been shown that aromatic amines can also be synthesized by reaction of cyclohexanone enolate with nitroarenes[14] or from enamines by using 3 equiv of a TiCl$_4$/Et$_3$N reagent system[15] or 2 equiv of a Pd^{II} complex.[16]

Here, we would like to report that aromatic amines can be obtained by dehydrogenation of enamines with a catalytic

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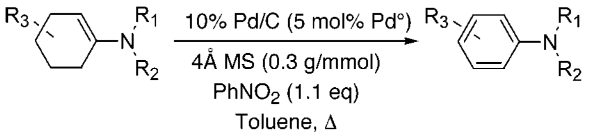
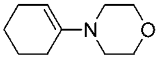
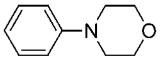
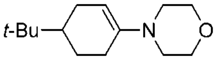
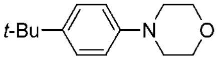
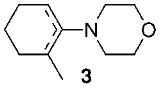
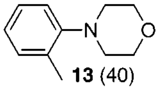
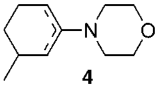
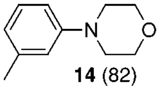
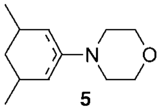
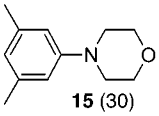
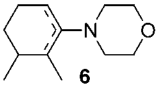
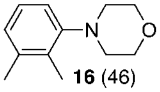
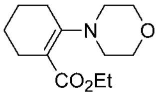
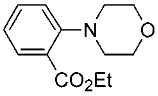
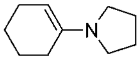
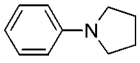
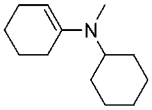
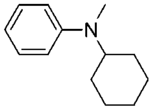
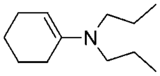
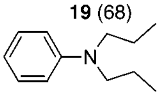
amount of 10% Pd/C (0.05 equiv of Pd^0), in the presence of nitrobenzene and 4 Å molecular sieves in refluxing toluene (Scheme 1).

Scheme 1



When enamine **1** was subjected to these conditions for 4 h, the aniline derivative **11** was isolated in 86% yield after purification by flash chromatography on silica gel (Table 1, entry 1). The aromatization reaction is general. A variety of morpholinoenamines, derived from substituted cyclohexanones such as 4-*tert*-butyl-, 2-methyl-, 3-methyl-, 3,5-dimethyl-, 2,3-dimethyl-, and 2-ethoxycarbonylcyclohexanone, were transformed to the corresponding substituted aniline derivatives in yields between 30% and 82% (Table 1, entries 2−7).

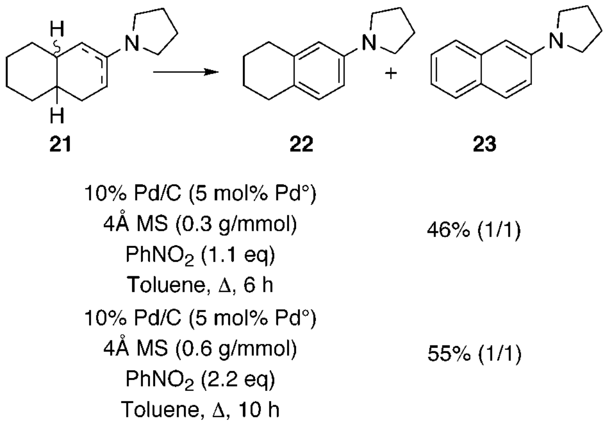
Table 1. Aromatization of Enamines

Entry	Starting Material	Time h	Product (Yield%)
1	 **1**	4	 **11** (86)
2	 **2**	5	 **12** (75)
3	 **3**	5	 **13** (40)
4	 **4**	5	 **14** (82)
5	 **5**	12	 **15** (30)
6	 **6**	7	 **16** (46)
7	 **7**	6	 **17** (30)
8	 **8**	5	 **18** (83)
9	 **9**	5	 **19** (68)
10	 **10**	4	 **20** (68)

It is worth noting that lower yields of aniline derivatives were obtained when the cyclohexenamines were substituted at C-2 or disubstituted. In addition, the present method can be applied to enamines prepared from cyclohexanone and pyrrolidine, *N*-methyl-*N*-cyclohexylamine, or *N*,*N*-dipropylamine. In each case, the enamines **8**−**10** were transformed to the corresponding aniline derivatives **18**−**20** in yields greater than 60% (Table, entries 8−10).

The pyrrolidinoenamine of 2-decalone, compound **21**, afforded a 1:1 mixture of compounds **22** and **23** in 46% yield. An increase of the number of equivalents of nitrobenzene (2.2 equiv) and the amount of molecular sieves, as well as the reflux time, slightly improved the yield, but the product ratio remained the same (Scheme 2).

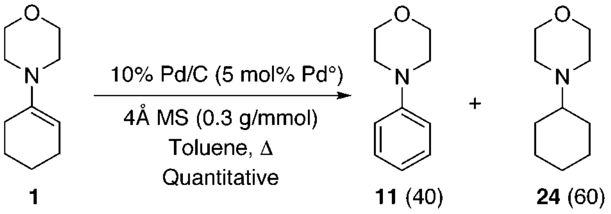
Scheme 2



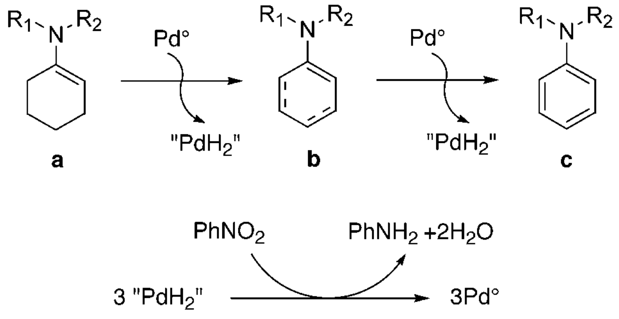
It is worth noting that treatment of **1** with 10% Pd/C (5 mol % of Pd^0) in the presence of 4 Å molecular sieves in refluxing toluene, but without nitrobenzene, produced a 40/60 mixture of **11** and morpholinocyclohexane **24** in quantitative yield (Scheme 3). This result shows that in the absence of nitrobenzene enamine **1** acts as the hydrogen acceptor and is reduced during the aromatization.

A plausible mechanism for this reaction is outlined in Scheme 4. When palladium(0) reacts with enamine **a**, a

Scheme 3



Scheme 4



dehydrogenation[9] takes place to produce diene **b** and palladium dihydride (“PdH_2”). The hydrogenation of nitrobenzene by PdH_2 effects the regeneration of Pd^0. The water that is liberated in this process is adsorbed on the molecular sieves, thus preventing hydrolysis of the enamine. Intermediate **b** can be aromatized to **c** by Pd/C, which is transformed to PdH_2 and again regenerated by hydrogenation of nitrobenzene.

In summary, we have developed a general, experimentally simple,[17] and inexpensive Pd^0 catalyst system for the synthesis of substituted anilines. This process, catalytic in palladium zero, provides efficient access to synthetically useful aromatic amines.

Supporting Information Available: References for spectroscopic data for compounds **11−20** and **22−24**. This material is available free of charge via Internet at http://pubs.acs.org.

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[17] Experimental procedure: To a solution of enamine (5 mmol)[18] in dry toluene (20 mL) were added 4 Å molecular sieves (1.5 g), dry nitrobenzene (0.57 mL, 5.5 mmol), and 10% Pd/C (0.27 g, 0.25 mmol of Pd^0). The resulting black mixture was stirred and refluxed for 4−12 h (GC/MS monitoring). After cooling to room temperature, the suspension was filtered through Celite, which was washed with AcOEt. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography on silica gel to give the aromatic amine.

[18] Hünig, S.; Lücke, E.; Brenninger, W. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 808−809.