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Reductive Amination of Ketones: Novel One-Step Transfer Hydrogenations

INTRODUCTION

Amines are indispensable building blocks in numerous drugs, pesticides, and colour pigments. Development of general and efficient methods to prepare amino compounds is still of high interest to the chemical industry. One of the most convenient methods to synthesize amines is the reductive amination of carbonyl compounds.

Nowadays, reductive transformations of ketones into amines are performed in the presence of catalysts. A wide range of metal-containing catalysts, usually as metal complexes, such as Pd, Ir, Rh, Ru and Ti are utilized in these processes.

Although some of these catalysts are widely used, they have limitations with regard to chemoselectivity, recyclability, safety, and costs.

Metals or metal-containing catalysts can be applied for reductive aminations with various reducing agents. In these processes, molecular hydrogen,[1-2] metal hydrides such as $NaBH_4$ or $NaBH_3CN$ or various transfer hydrogenating agents such as Hantzsch esters[3] can serve as the reducing agents.

Ammonium formate is an inexpensive, non-toxic, and environmentally safe reagent, and could serve as both the nitrogen source and the transfer hydrogenating agent simultaneously[4,5].

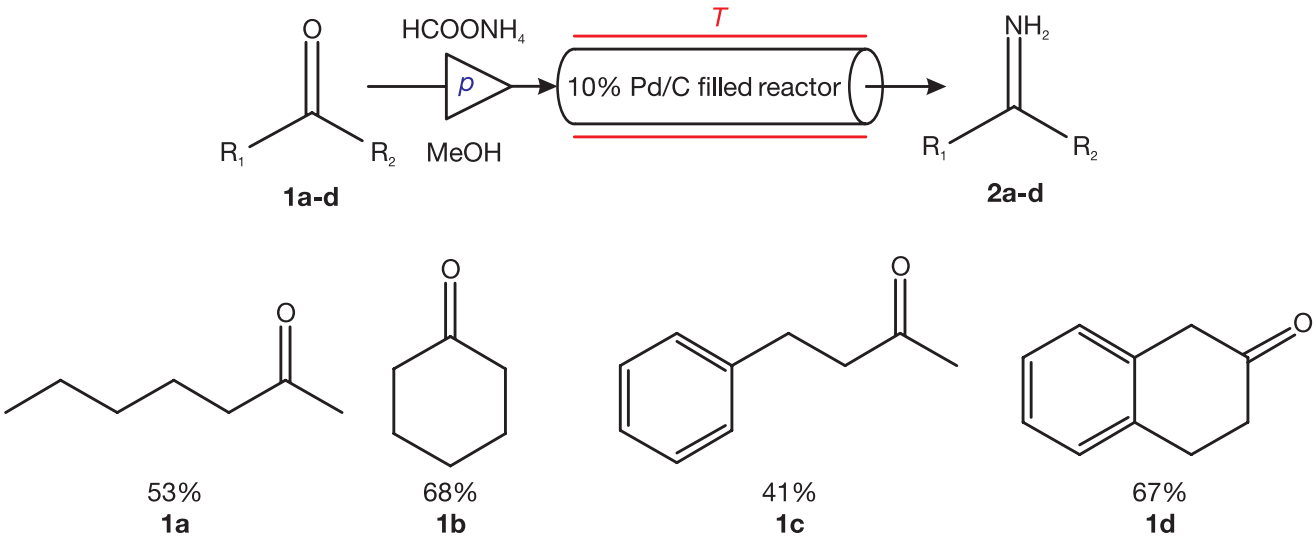
Ammonium formate was successfully applied previously in metal complex catalyzed or Pd/C-catalyzed[6] reductive aminations of ketones.

The reductive amination of ketones was investigated with ammonium formate and various metals/metal catalysts in one-pot and one-step reactions using both batch and continuous-flow methods.

RESULTS OF FLOW TRANSFER HYDROGENATION

We investigated the application of these methods for the reductive amination of ketones in continuous-flow systems using the X-Cube™ flow reactor.

In all cases, similar or higher yields of the amine were obtained compared to the corresponding batch reaction (53% vs 52% for **2a**; 68% vs 60% or 65% for **2b**; 41% vs 38% for **2c** and 67% vs 64% for **2d**).



Reductive aminations of aliphatic and cycloaliphatic ketones **1a–d** were carried out with the continuous flow system using a packed-bed column containing 10% Pd/C (6 equiv. of $HCOONH_4$ and 5 mg/mL of ketones **1a–d** in methanol; 40 °C; 0.2 mL/min; no measurable back-pressure). After the stationary state was reached (8 times dead volume of the column, 40 min), feeding the reactor with the corresponding ketones **1a–d** proceeded for 6 h. The amines **2a–d** were isolated from the collected homogeneous solutions.

The reactions were repeated for ketones **1a–d** in a second series of reductions on the same 10% Pd/C-filled column resulting in the same yields of products **2a–d**. The same catalyst column was used for at least 56 h of continuous reaction time with no catalyst deactivation observed. Therefore, the main advantage of the continuous flow system with 10% Pd/C-columns is the recyclability and the efficient, safe and reproducible use of the catalyst for an extended period of time, resulting in a more environmentally friendly process.

CONCLUSION

Retention of the homogeneous phase for the 10% Pd/C-catalyzed transfer hydrogenations of aliphatic and cycloaliphatic ketones **1a–d** allowed the recyclable, efficient, and reproducible use of this catalyst in a continuous flow reactor[7].

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