

Flow Hydrogenation; a Tool for Creating 3D-Shaped Molecules from Flat Precursors

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In this poster we present the efficient and convenient flow synthesis of mono- and disubstituted piperidine derivatives from their aromatic precursors. Rapid catalyst and condition screening was done in the automated H-Cube[®] flow reactor system equipped with a CatCart Changer[™] module. The optimized conditions were used as a general procedure to synthesize analogous structures using H-Cube Autosampler[™]. Diastereoselectivity in the reduction of disubstituted pyridine species has also been investigated.

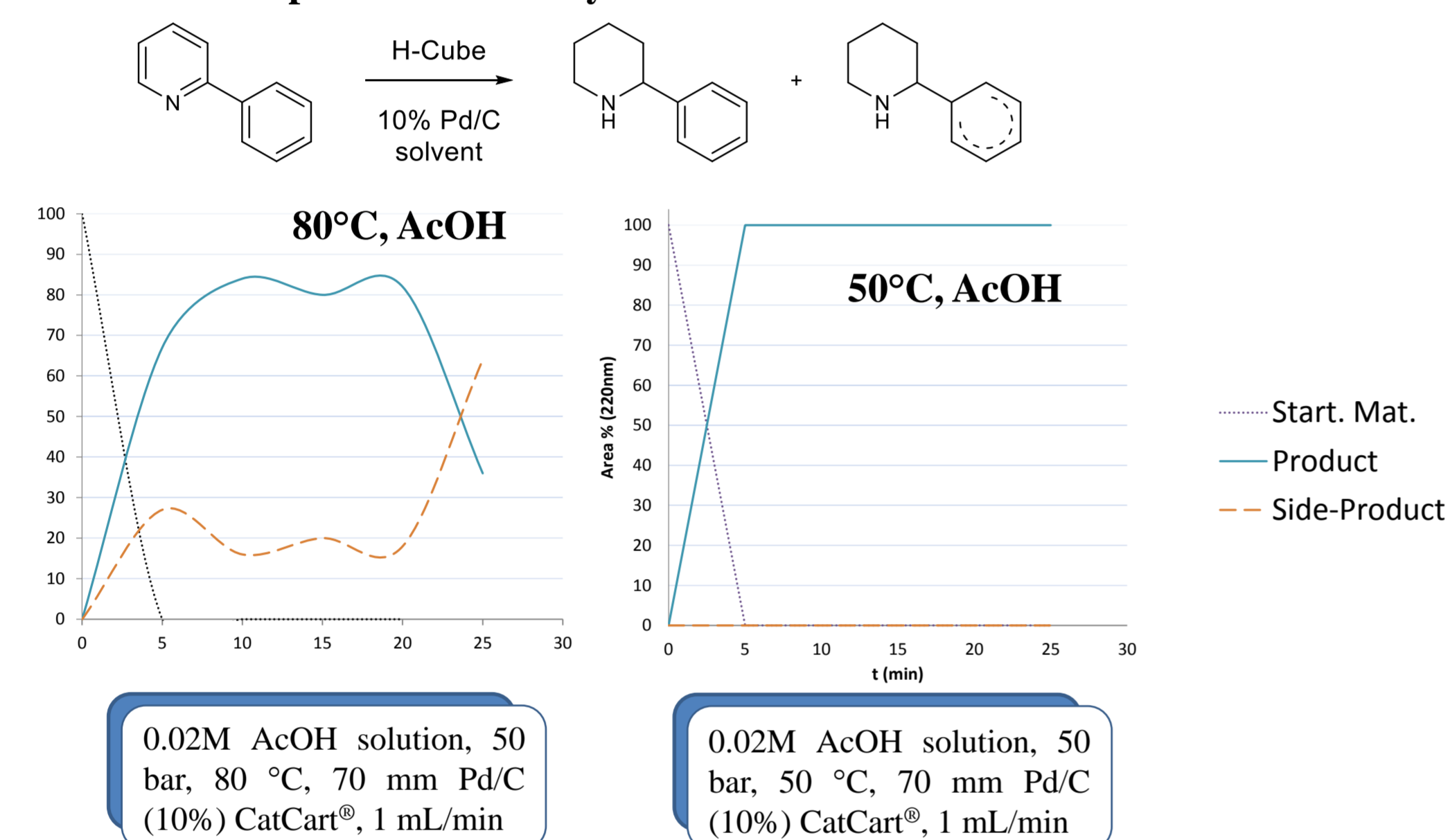
Introduction

Due to high-throughput synthetic practices over the past decades the number of achiral, aromatic compounds tremendously increased in compound libraries. Too many aromatic rings present higher attrition rate in the drug pipeline, and the diversity of shapes in the set of known 2D-shaped drugs is extremely low,¹ thus the need for the design and synthesis of non-flat molecules having more advantageous properties is increasing.² Complexity as measured by fsp3 (fraction of sp3 carbons) and the presence of chiral centers correlate with success as compounds transition from discovery, through clinical testing, to drugs.³ New 3D-shaped templates could easily be generated *via* simple reduction of flat aromatic precursors. Reduction is difficult to automate and it suffers from inconveniences under batch conditions. This hurdle can be overcome by the use of flow hydrogenation reactors

Results and Discussion

Moderate conversion and/or product selectivity has been observed in the reduction of mono-substituted pyridines in ethylacetate and alcohols. The selectivity was increased in glacial acetic acid. This observation is in accordance with the theory claiming that the faster rate of hydrogenation could be due to flat absorption of the pyridinium ion on the catalyst surface, whereas the free base may absorb edgewise. Thus, all experiments were performed exclusively in glacial acetic acid in 0.02M concentration. Although vast variation of catalysts (Pd/C, PtO₂, Pt/C, Rh/C, Ru/C, Pd(OH)₂) were tested, finally 10% palladium on carbon was selected for further experiments due to better results achieved and cost saving considerations. Product selectivity was highly dependent on the applied temperature. The best product selectivity was obtained at 50 °C thus for further reductions these optimized conditions were applied.

Temperature effect on product selectivity



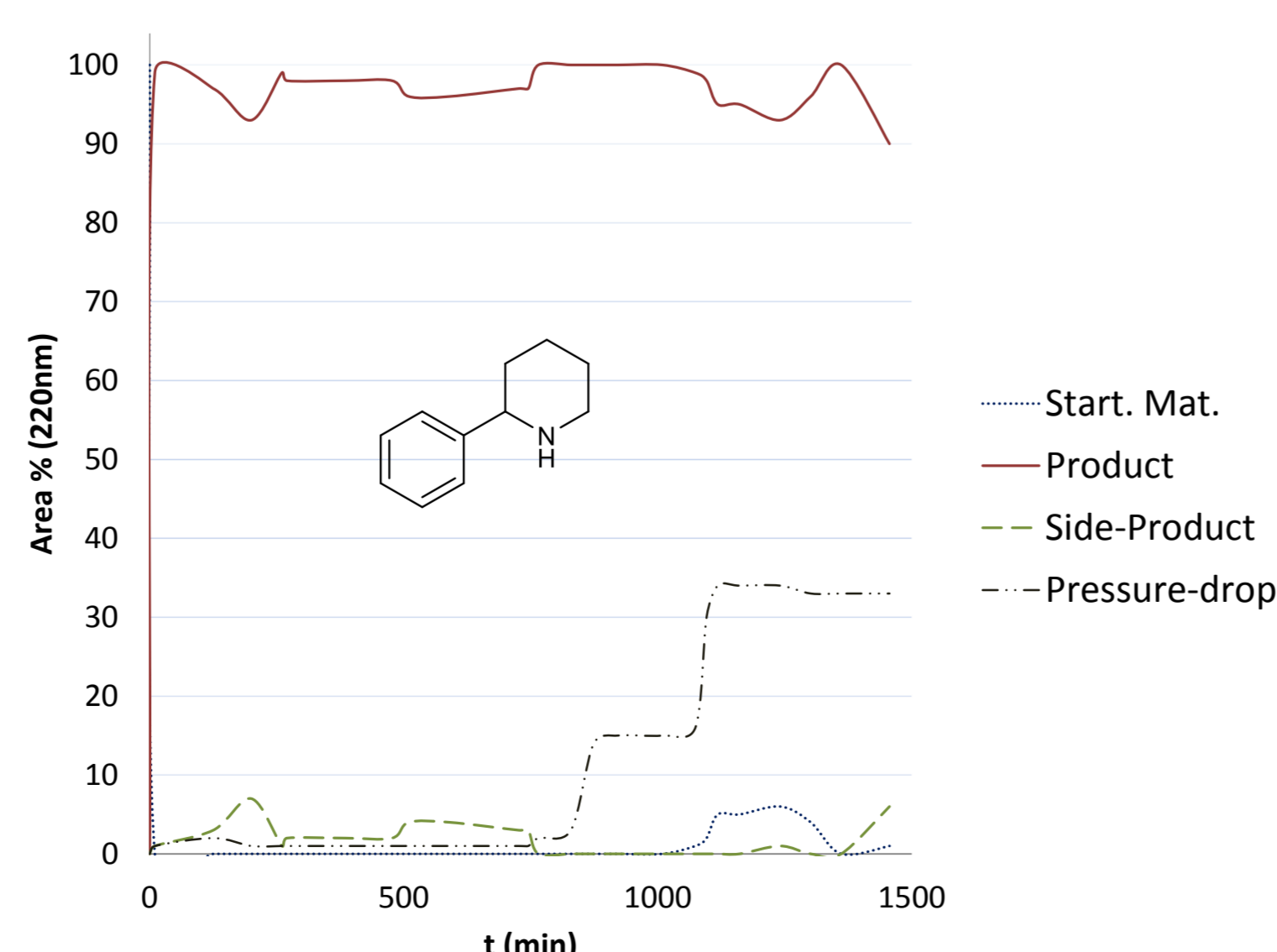
Effect of substitution was investigated among various mono substituted pyridines. No connection was observed between the rate of hydrogenation and the electronic character of the substituents.

Starting Material	Product	Conversion (%)	Selectivity (%)
1 ^a		100	100
2 ^a		100	100
3 ^a		85	100
4 ^a		100	>95 ^b
5 ^a		100	>95 ^b
6 ^a		100	100
7 ^a		100	100
8 ^a		60	100
9 ^a		100	100

^a 0.02M AcOH solution, 50 bar, 50 °C, 70 mm Pd/C (10%) CatCart[®], 1 mL/min. ^b Selectivity vs. over-saturated side-product.

Scale-up results

A 0.02M solution of 2-phenylpyridine was reduced in an H-Cube[®] flow system through a 70 mm long cartridge filled with *ca.* 250 mg catalyst. Noticeable activity decrease was observed after the reduction of *ca.* 4.5g material. Pressure deviance caused only by the HPLC pump. This good catalyst longevity makes the synthesis of fragment-like libraries cost-effective.

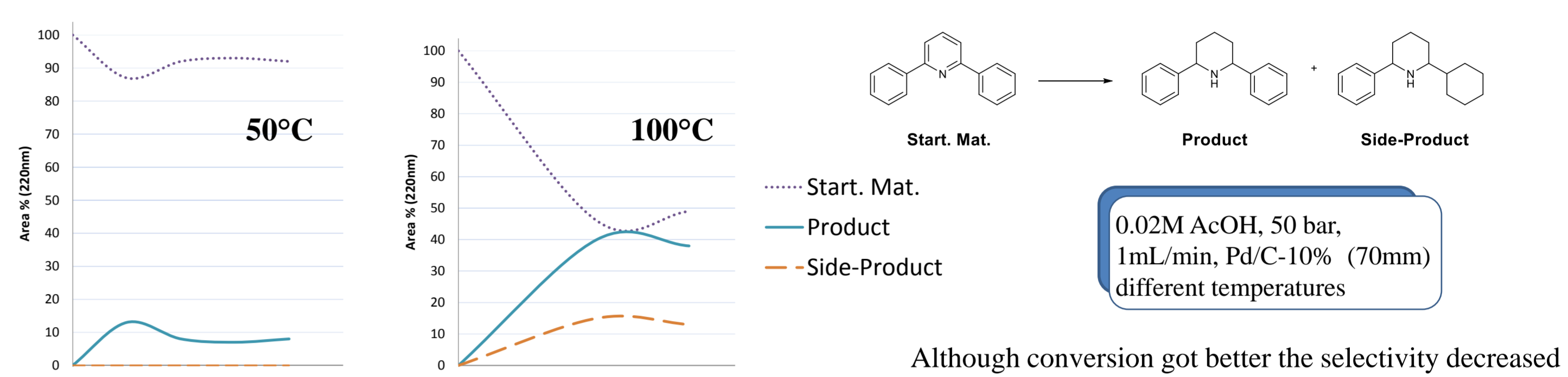


References

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- 2 Ritchie, T. J.; Macdonald, S. J. *DDT*, **2009 Nov**, *14*(21-22), 1011.
- 3 Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.*, **2009**, *52*, 6752.
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Disubstituted pyridines

Reduction of bulky and flat diphenyl substituted pyridines furnished the desired products in low yields even under harsh conditions. Moderate hydrogenation rate enhancement could be reached only by increasing the temperature to 100 °C but no significant difference was observed when switching from palladium catalyst to the more active platinum. Among diphenylpyridine analogues slightly better hydrogenation rates have been observed for 3,5- and 3,4-diphenylpyridines than for 2,4-, 2,5- and 2,6- diphenylpyridines.



Less bulky disubstituted pyridine derivatives could easily be saturated furnishing the desired piperidine derivatives. Reductions were done at elevated temperature (80 °C) on Pd/C catalyst with 100% conversion and excellent product selectivity. In most reductions a major stereoisomer was received in moderate to good stereoselectivity. The relative configurations were determined by 2D and ¹³C NMR experiments⁴.

Starting Material	Product	Conversion (%)	Selectivity (%)	cis/trans (%)
1 ^a		100	90	100/0
2 ^a		100	85	60/40
3 ^a		100	95	70/30
4 ^a		100	65	80/20

^a 0.04M AcOH solution, 50 bar, 80 °C, 70 mm Pd/C (10%) CatCart[®], 1 mL/min

Mono-substituted quinoline derivatives have also been readily saturated on palladium catalyst with very good selectivity. Sometimes reduction of these type of skeletons takes place under mild conditions. The investigation of the reduction of disubstituted quinoline analogues is in progress.

Starting Material	Product	Conversion (%)	Selectivity (%)
1 ^a		85	good
2 ^b		70	>95
3 ^c		100	>95

^a 0.02M AcOH solution, 50 bar, 100 °C, 70 mm Pd/C (10%) CatCart[®], 1 mL/min. ^b 0.02M AcOH solution, 50 bar, 50 °C, 70 mm Pd/C (10%) CatCart[®], 1 mL/min. ^c 0.02M AcOH solution, atm. H₂ pressure, 25 °C, 70 mm Pd/C (10%) CatCart[®], 1 mL/min

Instrumentation

The H-Cube[®] flow reactor system equipped with a CatCart Changer[™] module was used for rapid solvent and catalyst screening. The reductions under the optimized conditions were done using the H-Cube Autosampler[™] that provides all benefits of the H-Cube[®] integrated with a liquid handler.



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Summary

We have developed a convenient and general approach for the reduction of pyridine analogues in the H-Cube[®] flow hydrogenation system. The developed methods can easily be scaled up producing high fsp3 containing fragments and/or scaffolds from readily available simple flat aromatic compounds. Pyridine derivatives were saturated with high selectivity to the appropriate piperidine derivatives. Moderate to good stereoselectivity was observed in most reductions of disubstituted pyridines. The extension of the method to more complex *N*-heterocycles is under investigation. Preliminary results showed that the conditions presented in this poster can be applied successfully to other ring systems as well.