Literature Report 9

The Partial Reduction of Pyridines: Route to 1,2- or 1,4-Dihydropyridines

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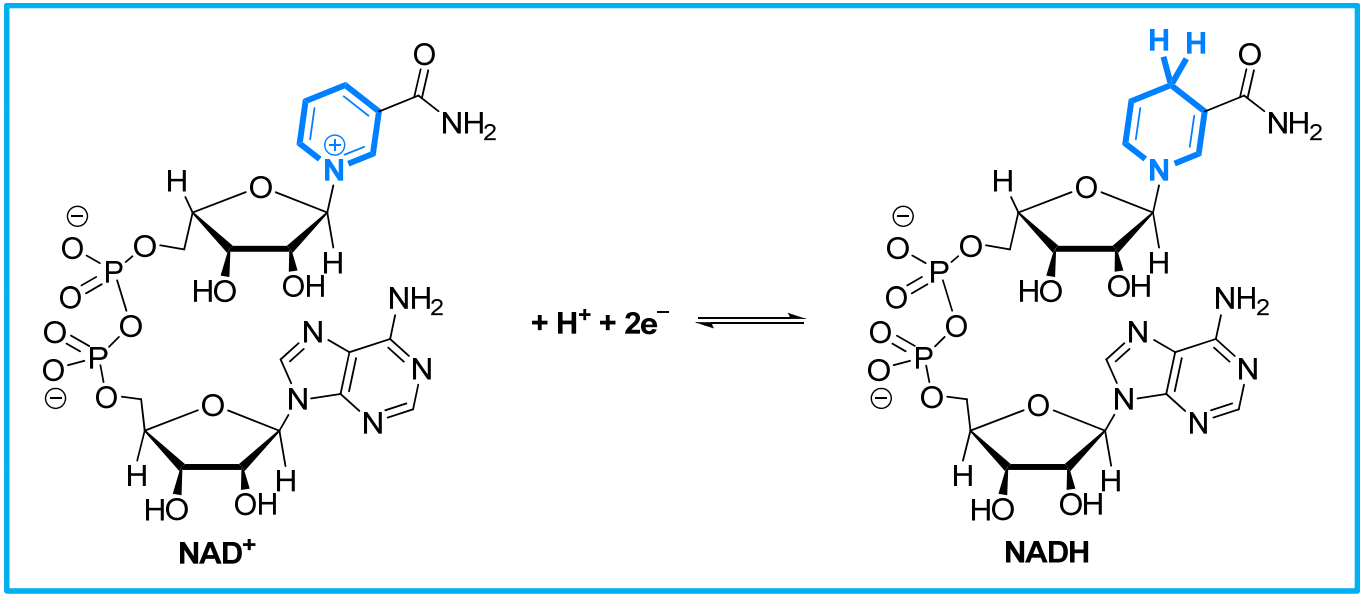
Checker： Lei Shi
Date: 2013/09/24

M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 10076.

目录

背景知识

烟酰胺腺嘌呤二核苷酸(NADH)：是一种传递氢离子的辅酶，它出现在细胞的许多代谢反应中。大部分涉及到氧化还原的反应都需要它，比如呼吸作用、光合作用等。



The structure of the redox pair: NAD^+ and NADH

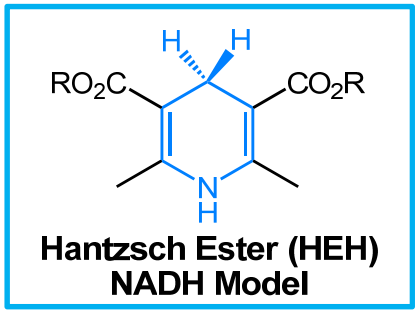
M. Ziegler, *Biochem. J.* **2007**, *402*, 205.

背景知识

将逆反应应用于有机反应中的例子 (仿生化学):

For reviews, see:

1) U. Eisner, *Chem. Rev*. **1972**, 72, 1.
2) D. M. Stout, *Chem. Rev.* **1982**, *82*, 223.
3) R. Lavilla, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1141.
4) J. C. Moore, *Acc. Chem. Res.* **2007**, *40*, 1412.
5) D.W. C. MacMillan, *Acc. Chem. Res*. **2007**, *40*, 1327.
6) S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498.



Hantzsch Ester (HEH)
NADH Model

For seminal original contributions, see:

6) M. Rueping, *Org. Lett*. **2005**, *7*, 3781.
7) B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424.
8) D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84.

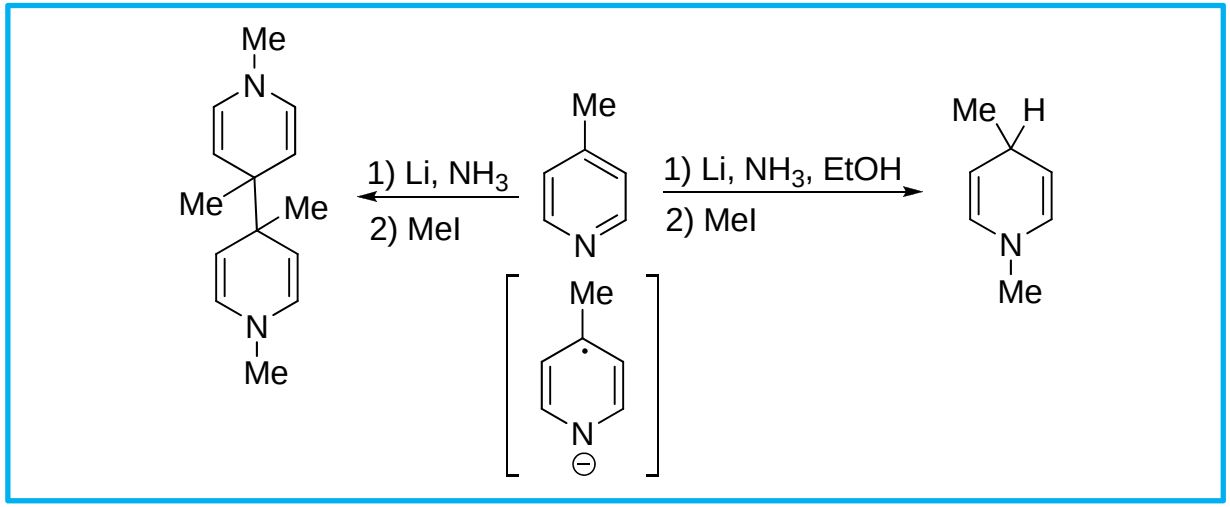
有机化学中的正反应难以发生：如何破坏高度稳定的吡啶环芳香性？

For a review on unconventional ways to regenerate 1,4- dihydropyridines from pyridinium ions, see:
F. Hollmann, *ChemCatChem* **2010**, *2*, 762.

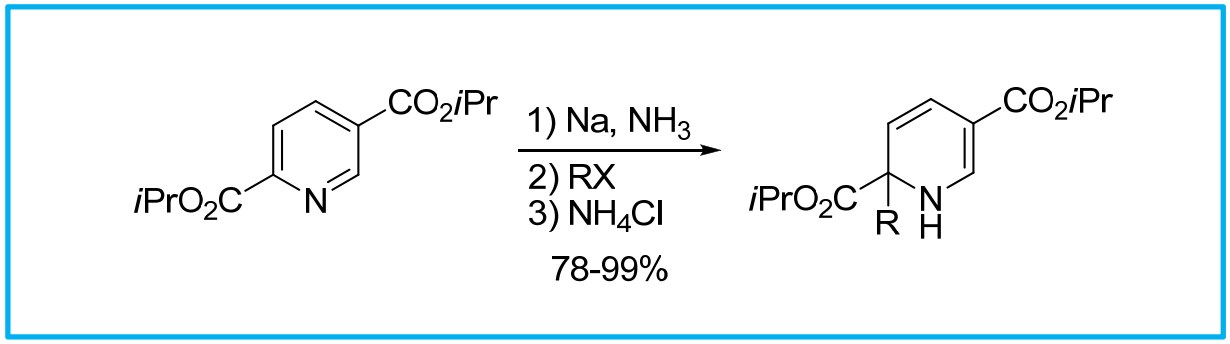
② 吡啶部分还原简介

1. 伯奇还原
   --Birch and Donohoe
2. 过渡金属催化氢化
   --Norton and Zhou
3. 硼氢化
   --Hill and Suginome
4. 硅硼化
   --Suginome
5. 硅氢化
   --Harrod, Nikonov, and Oestreich

伯奇还原

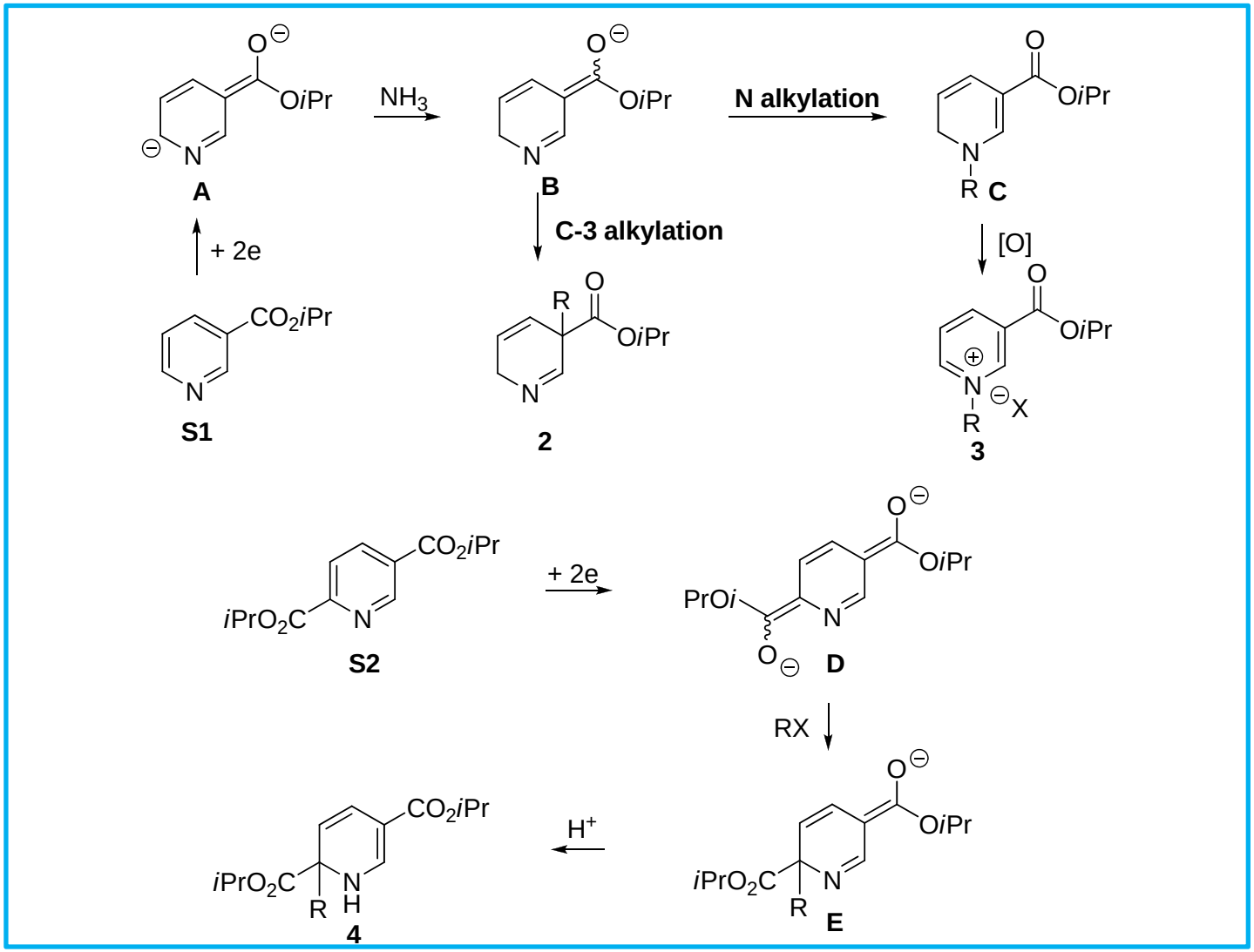


A. J. Birch, *J. Chem. Soc., Chem. Commun*. **1975**, 480.



T. J. Donohoe, *Org. Lett*. **2000**, *2*, 3861.
T. J. Donohoe, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435.

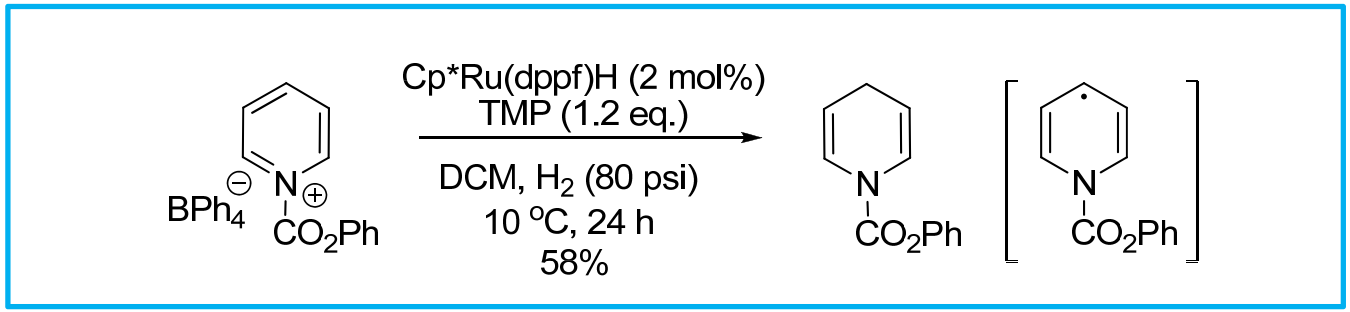
伯奇还原



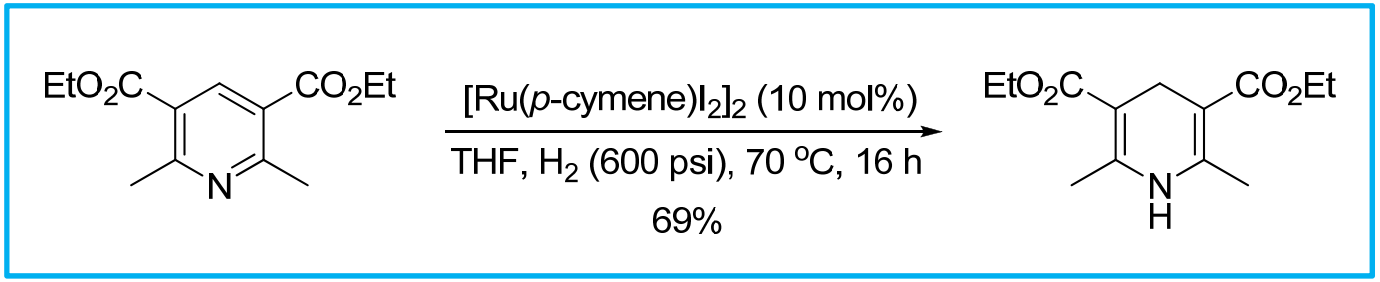
T. J. Donohoe, *Org. Lett*. **2000**, *2*, 3861.

T. J. Donohoe, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435.

过渡金属催化氢化

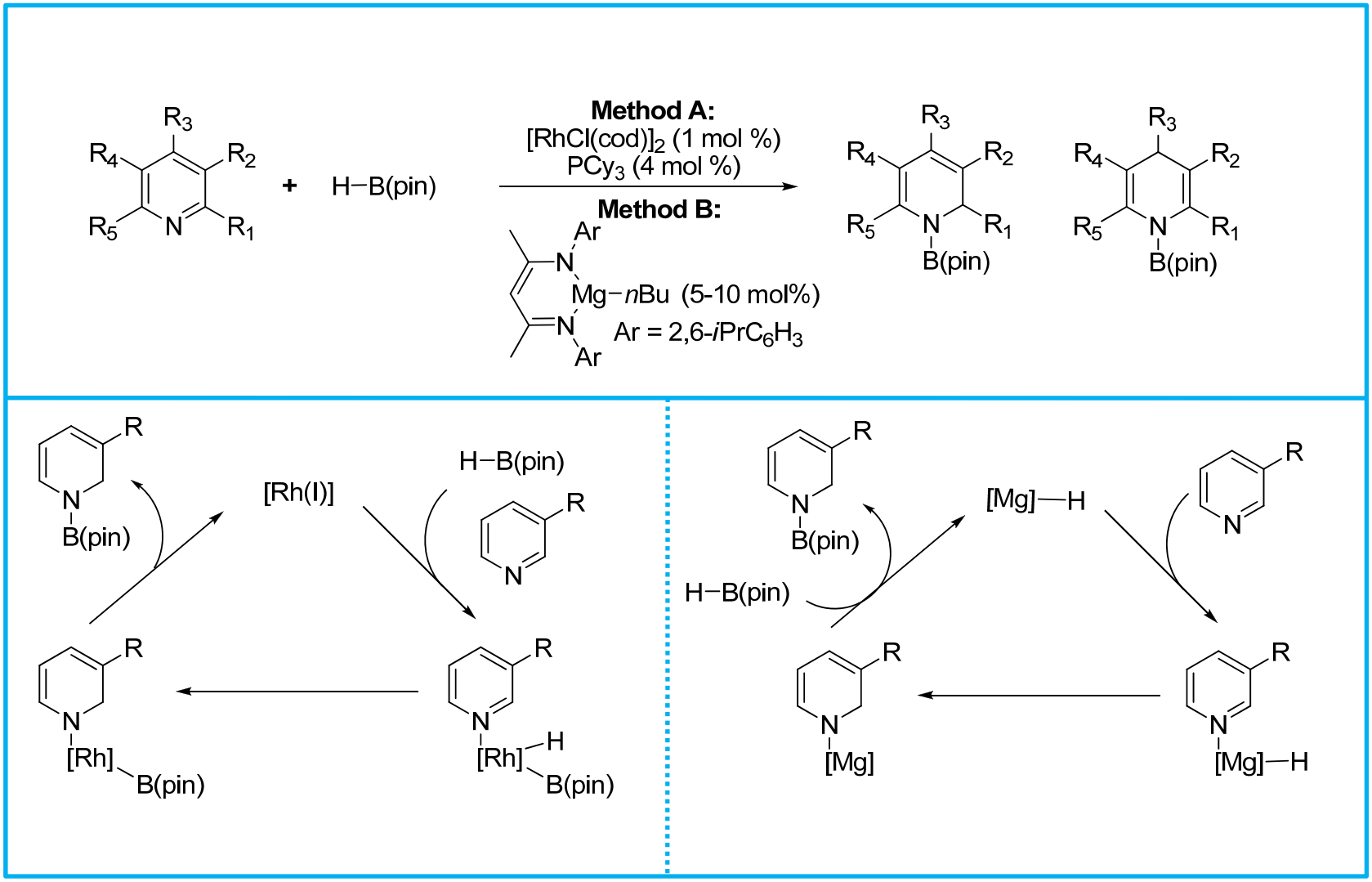


J. R. Norton, *J. Org. Chem*. **2008**, *73*, 9668.



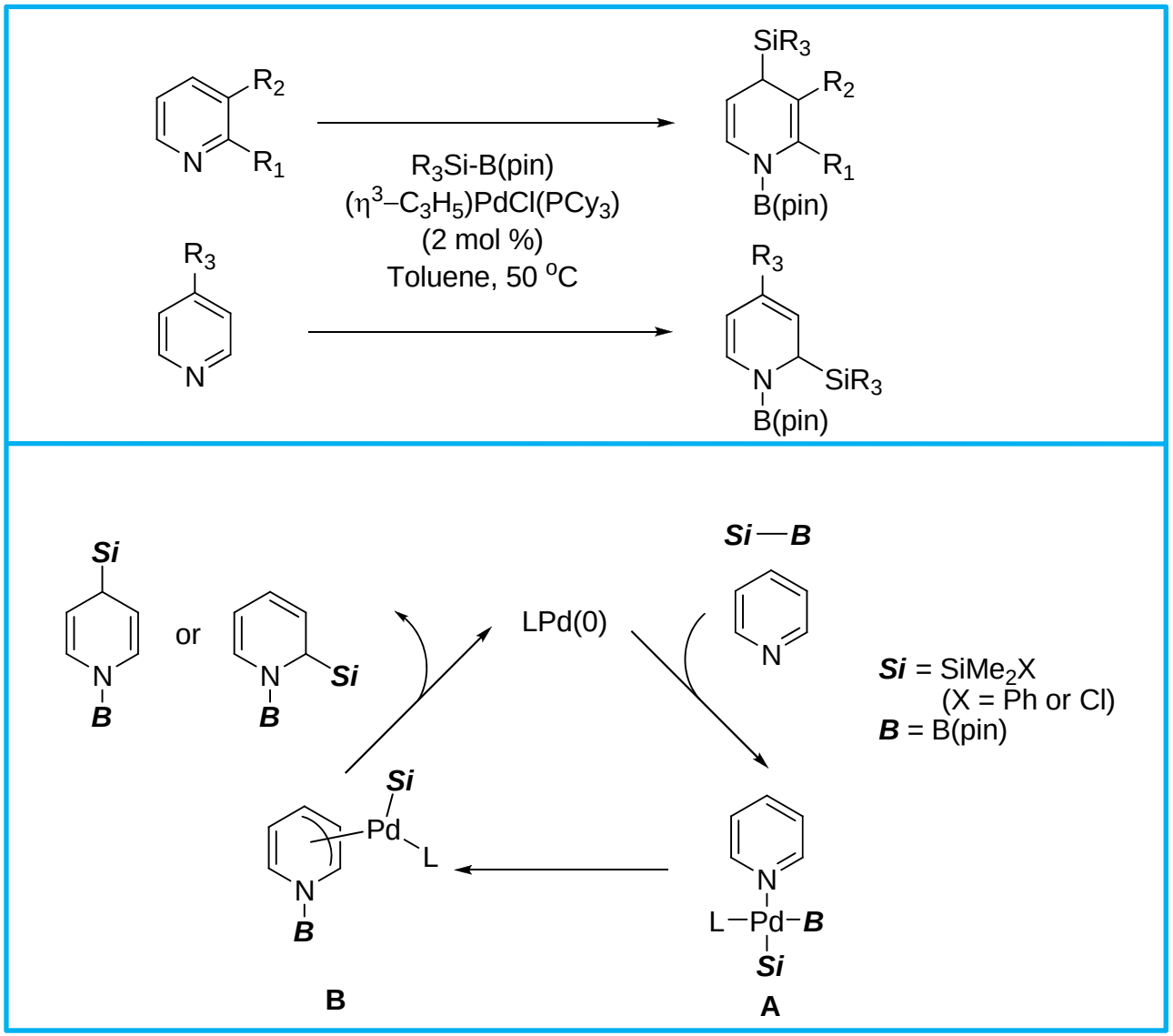
Y.-G. Zhou, *J. Am. Chem. Soc*. **2011**, *133*, 16432.

③ 硼氢化



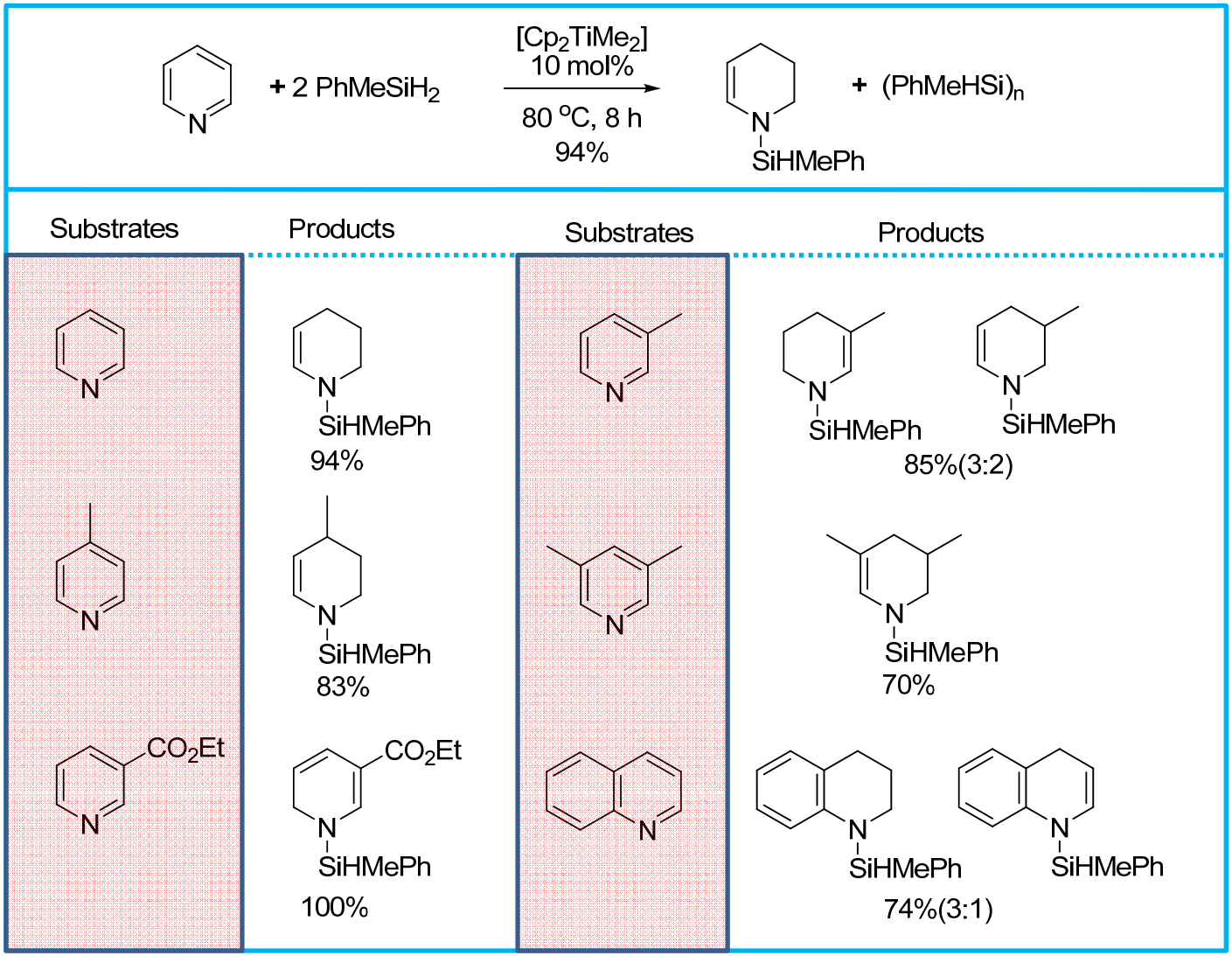
M. S. Hill, *Organometallics* **2011**, *30*, 5556.
M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 3699.

③ 硅硼化



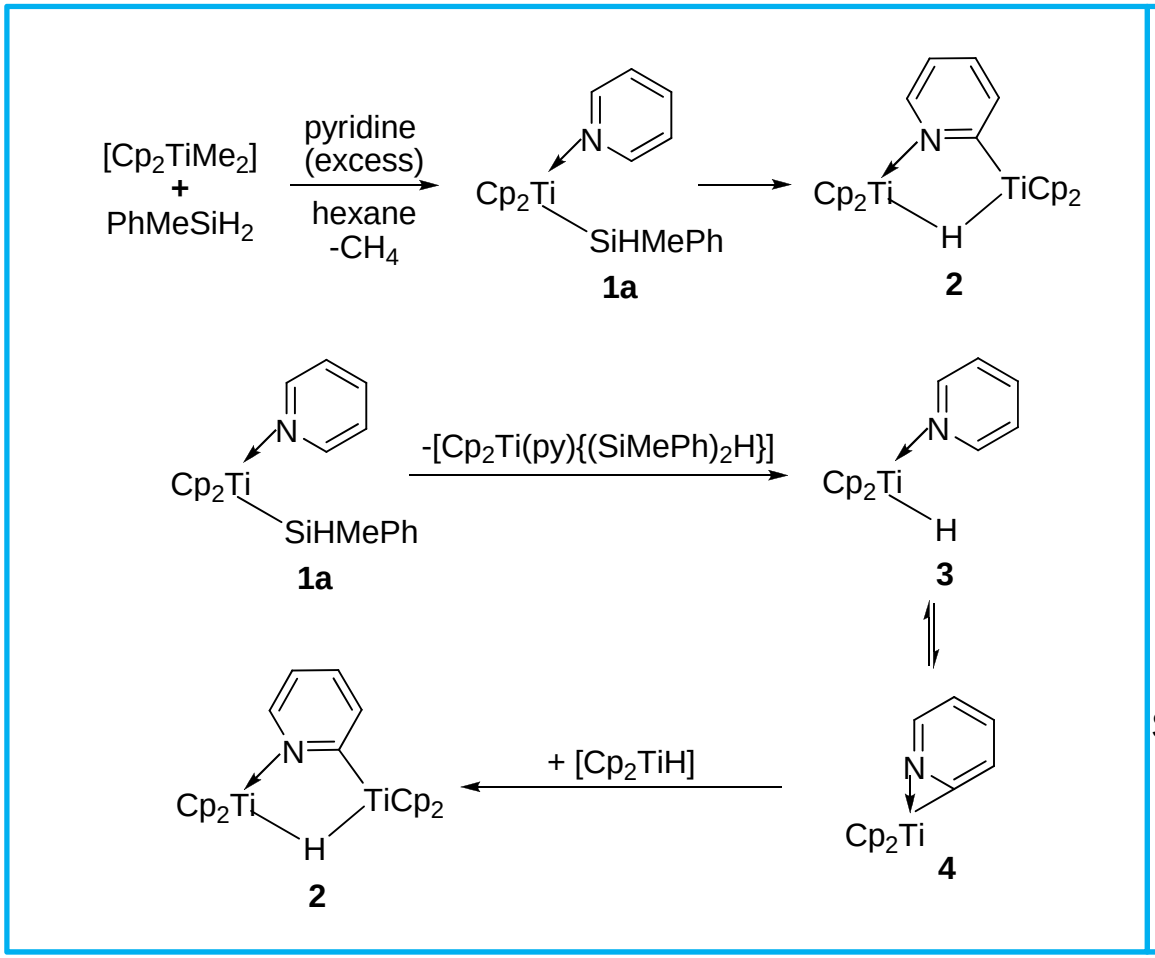
M. Suginome, *J. Am. Chem. Soc*. **2011**, *133*, 7324.

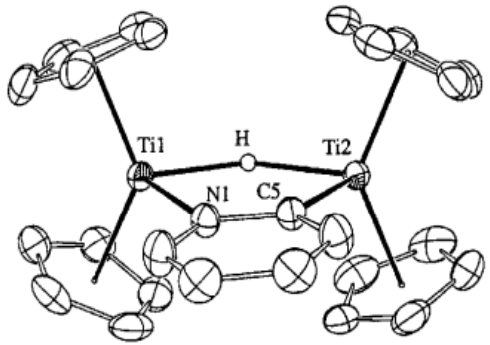
4 硅氢化



J. F. Harrod, *Angew. Chem. Int. Ed*. **1998**, *37*, 3126.
J. F. Harrod, *Can. J. Chem*. **2001**, *79*, 1075.

4 硅氢化

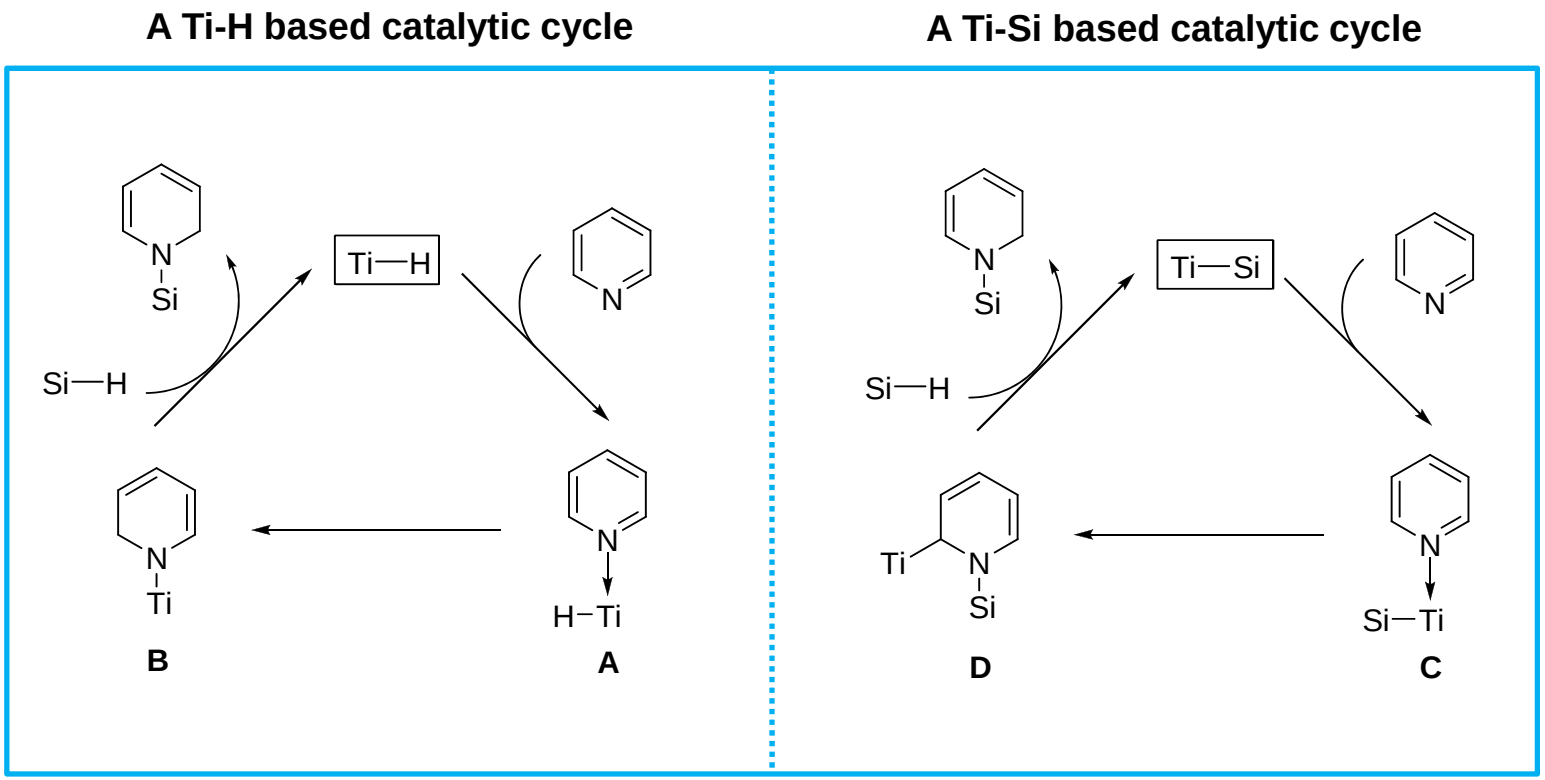




Single-Crystal X-ray Structure of **2**

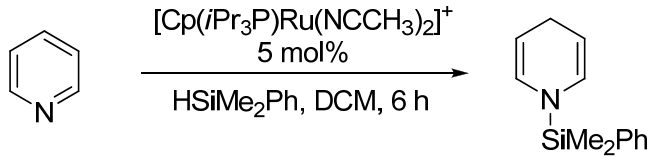
J. F. Harrod, *Angew. Chem. Int. Ed*. **1998**, *37*, 3126.
J. F. Harrod, *Can. J. Chem*. **2001**, *79*, 1075.

4 硅氢化-氢化



J. F. Harrod, *Angew. Chem. Int. Ed*. **1998**, *37*, 3126.
J. F. Harrod, *Can. J. Chem*. **2001**, *79*, 1075.

4 硅氢化



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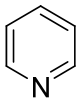
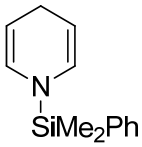
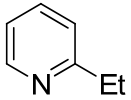
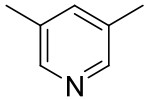
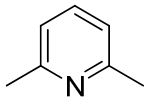
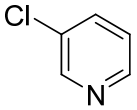
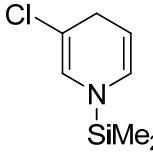
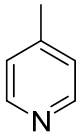
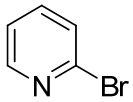
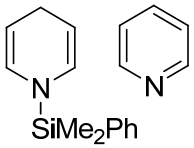
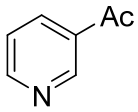
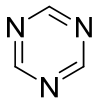
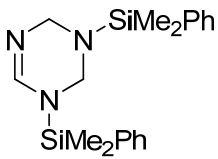
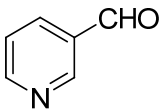
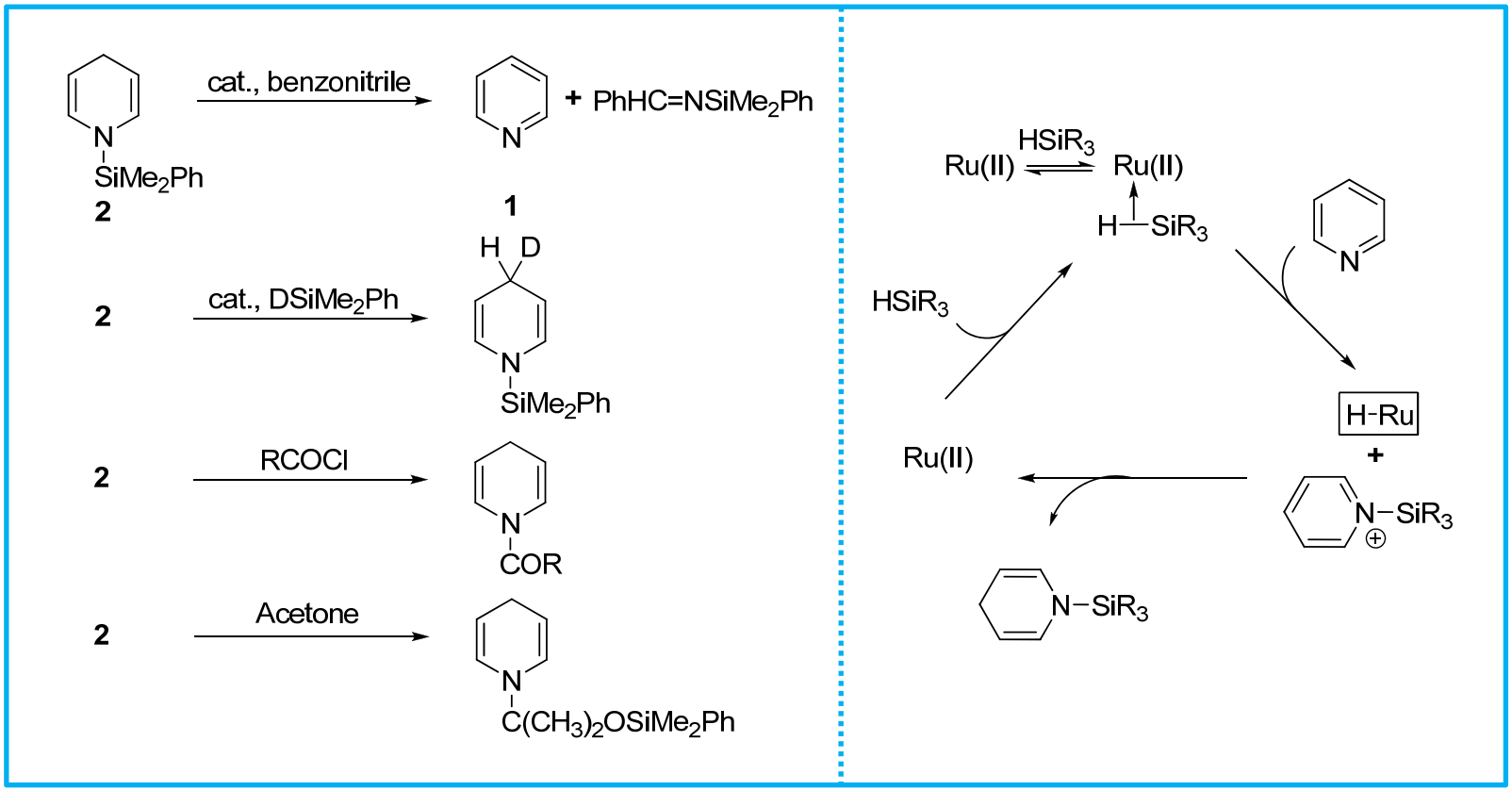
	86	0.5			0	3	-
	82	3			0	24	-
	100	0.25			0	24	-
	47	3			100	0.5	Mixture
	98	3.5			100	0.5	Mixture

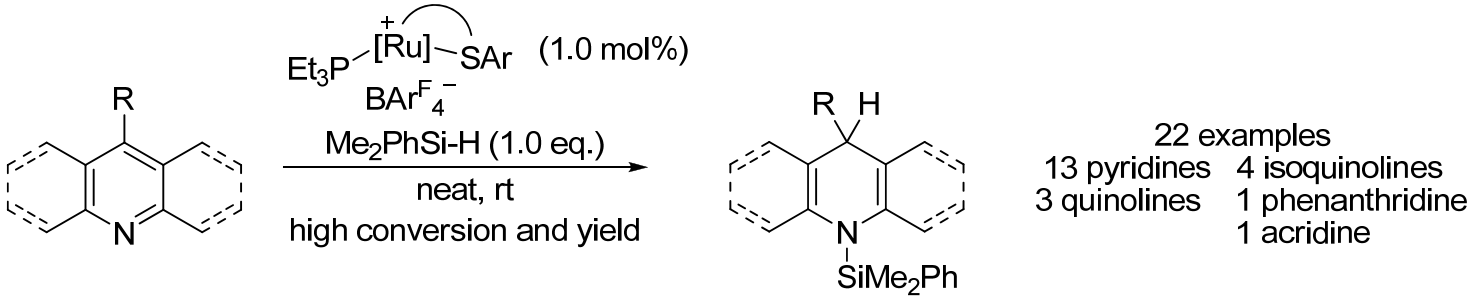
G. I. Nikonov, *Angew. Chem. Int. Ed*. **2011**, *50*, 1384.
Highlighted by K. Osakada, *Angew. Chem. Int. Ed*. **2011**, *50*, 3845.

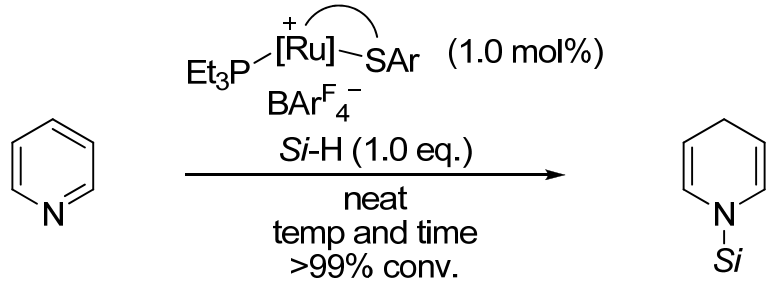
硅氢化



G. I. Nikonov, *Angew. Chem. Int. Ed*. **2011**, *50*, 1384.
Highlighted by K. Osakada, *Angew. Chem. Int. Ed*. **2011**, *50*, 3845.

硅氢化– Oestreich

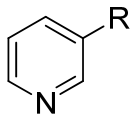




Entry	Silane Si-H	T (ºC)	T (h)	Yield (%)
1	Me_2PhSiH	RT	7	94
2	$MePh_2SiH$	45	14	96
3	$EtMe_2SiH$	RT	7	84
4	Et_3SiH	60	14	--
5	Ph_3SiH	60	14	--

M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 10076.

硅氢化– Oestreich

Entry	Substrate		Product	Yield (%)
1		R = Me		84
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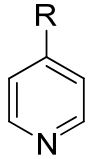
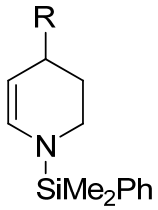
3		R = Br		96
4		R = Cl		76
5		R = F		76
6		R = Me		80
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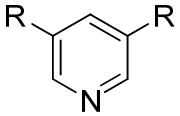
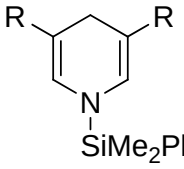
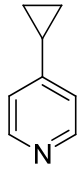
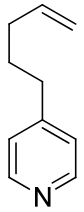
10		R = Ph		13
11		R = Cl		--
12		R = Me		80
13		R = Cl		98
14		R = F		84

radical clocks



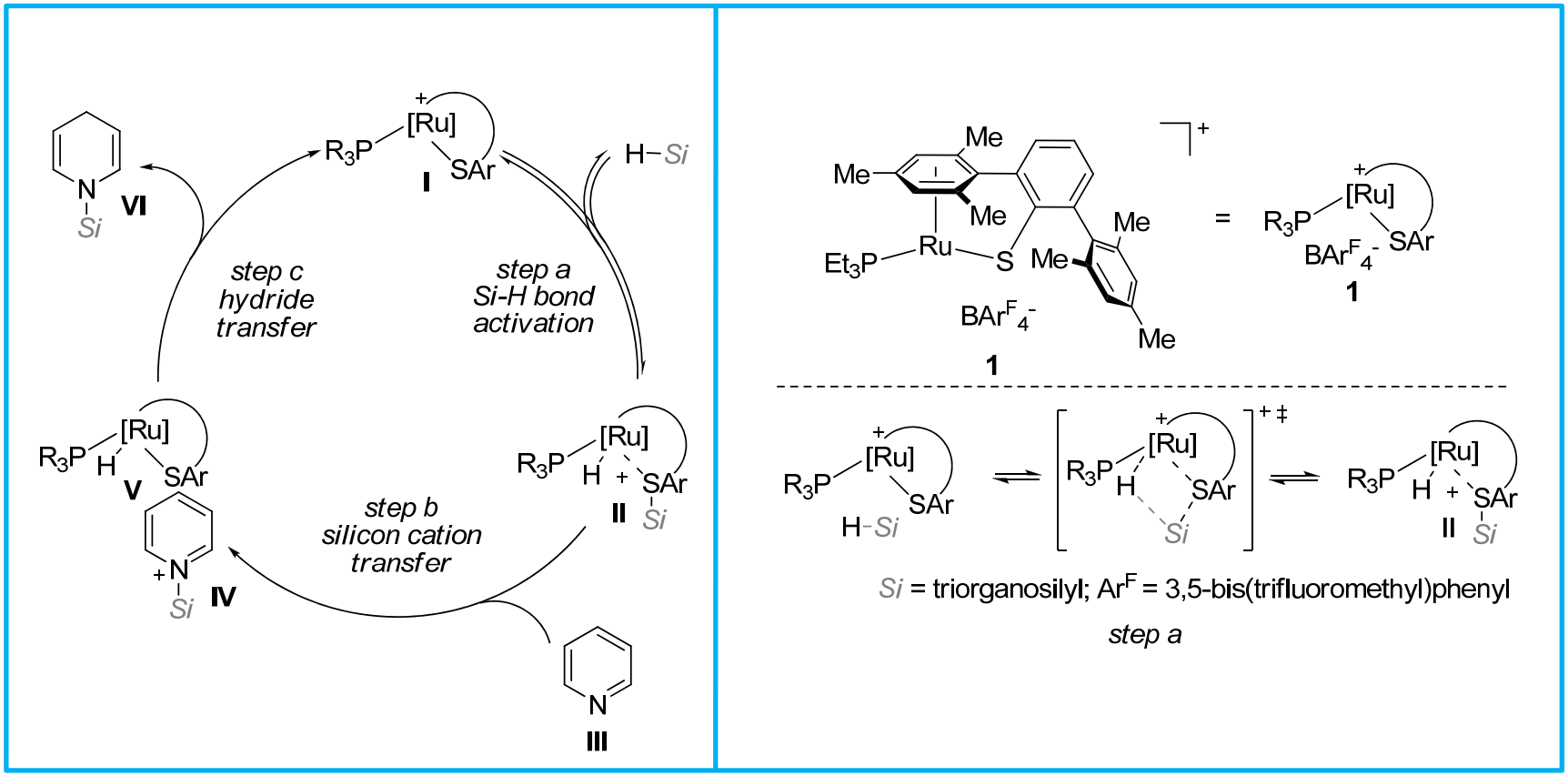
6% conversion
to 1,4-dihydropyridine
no ring opening



17% conversion
to 1,4-dihydropyridine
no spirocyclization

M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 10076.

硅氢化– Oestreich



M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 10076.

5 总结与讨论

John F. Harrod
Department of Chemistry
McGill University

底物范围较窄，选择性差，且有过度加氢副产物，催化剂用量大，条件剧烈。
第一例均相金属催化的芳香化合物的硅氢化反应，且对机理做了大量研究性工作。

Georgii I. Nikonov
Department of Chemistry
Brock University

底物范围相对仍较窄。

选择性高，反应可逆，条件温和。

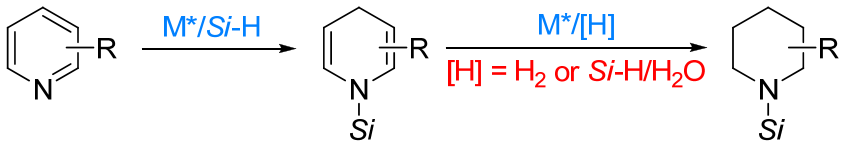
Martin Oestreich
Institut für Chemie
Technische Universität Berlin

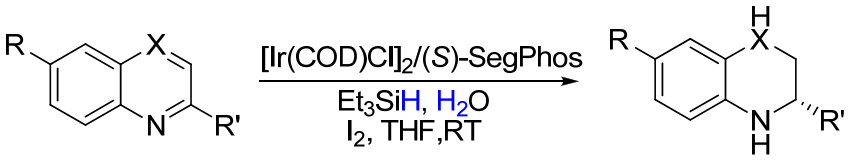
底物范围拓宽至其他芳杂环。
反应条件温和，选择性和转化率高。
排除了SET机理。

总结与讨论

过渡金属催化的芳香杂环化合物，其氢化难点主要有：
芳香性需要较高能量破坏；
产物中的N,S杂原子容易毒化催化剂降低催化效率。

是否可以将金属催化的硅氢化反应与氢化相结合，以接力催化的方式完成对底物的完全氢化。硅氢化启动还原反应第一步：硅氢化启动条件温和，且N-Si键可以阻断杂原子与催化剂的配位。氢化反应通过手性配体控制产物立体结构。这样可以解决单过渡金属+氢气体系中需要面对的两大难题。





X = CH, N

Up to 93% ee

Y.-G. Zhou, *Chem. Eur. J.* **2010**, *16*, 1133

问题：硅氢化-氢化反应将反应转化为硅氢化和C=C键的加氢，与以往转化为C=N键加氢不同。可能需要对金属和反应条件进行重新筛选。

The NAD(P)H/NAD(P)+ redox cycle with its 1,4-dihydropyridine/pyridinium ion interconversion is one of the fundamental transformations in biological systems. Outside living organisms, the forward reaction, that is, reduction through oxidation of the 1,4-dihydropyridine, is straightforward, and the use of 1,4-dihydropyridines as reducing agents in organocatalysis is a prime example of that. The back reaction poses, however, a remarkable challenge, and there is, to date, no general method available for the partial reduction of pyridines. The notion that breaking the aromaticity of pyridines by a Birch-type reduction to provide an entry to synthetically useful building blocks was realized close to a century ago. Birch and Karakhanov later investigated these reductions with solvated electrons more systematically with limited success, and it was only recently that Donohoe and co-workers demonstrated the potential of this method for a few selected systems. Another obvious approach is the partial hydrogenation of pyridines with dihydrogen under transition-metal catalysis, but the problem of over reduction of the more reactive enamine intermediate remains unsolved.

Recently, the Hill and Suginome groups independently introduced a noteworthy alternative strategy that allows for partial reduction of pyridines, either by magnesium(II)- or rhodium(I)-catalyzed hydroboration. Prior to these seminal contributions, homogeneous hydrosilylation of pyridines had been probed by Harrod and co-workers with a titanocene(III) catalyst but the chemoselectivity was moderate. Aside from this isolated report, the unsolved challenge had lain dormant for another decade until Nikonov and co-workers disclosed a pyridine hydrosilylation using cationic ruthenium(II) complexes $[Cp\text{-}(i Pr_3P)Ru(MeCN)_2]^+ X$ [X = PF_6 or $B(C_6F_5)_4$; Cp = Cyclopentadienyl]. The scope of this catalysis was, in the end, relatively narrow, but a few pyridines reacted 1,4-selectively at room temperature, and that certainly was a major step forward. Despite these recent significant advances in pyridine hydroboration and hydrosilylation, the latter methods are still far from being general.

The present method provides a viable tool for the chemo and regioselective hydrosilylation of various pyridines and related nitrogen-containing heterocycles. Using equimolar amounts of substrate and silane at low catalyst loading, the reactions are exceptionally clean (aside from $(Me_2PhSi)_2O$ contamination at incomplete silane consumption in a few cases) and do not require complicated purification of partially saturated heterocycles susceptible to oxidation. The pronounced 1,4-selectivity in the hydrosilylation of pyridines and quinolines is likely achieved in an ionic one-step hydride transfer onto the pyridinium/quinolinium ion intermediate, and that distinguishes the present work from previous reports of a radical mechanism.

谢谢大家！