Reductive and Transition-Metal-Free: Oxidation of Secondary Alcohols by Sodium Hydride

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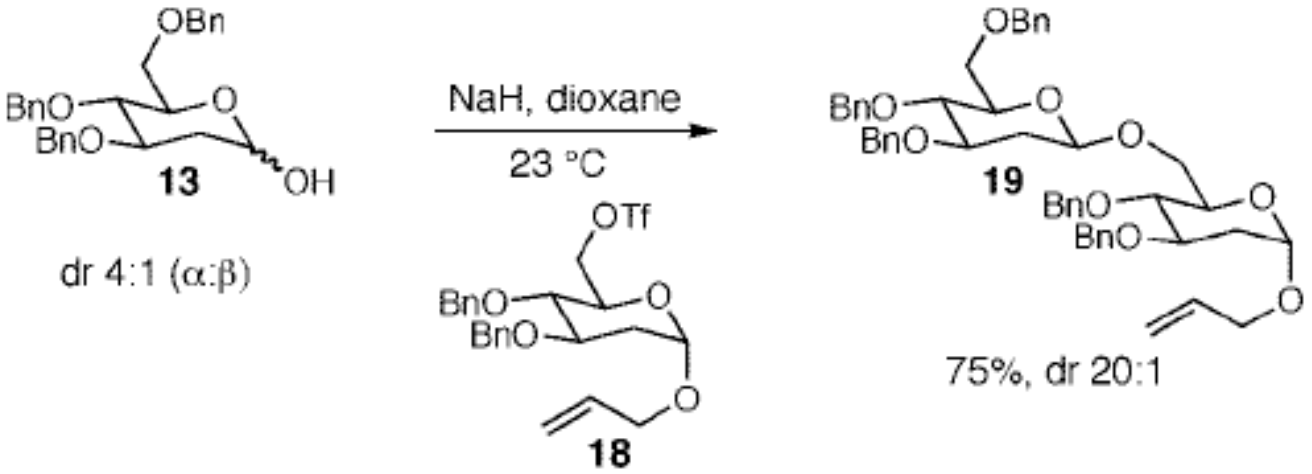
Group Meeting Presentation

The Wulff Group

Anil Kumar Gupta

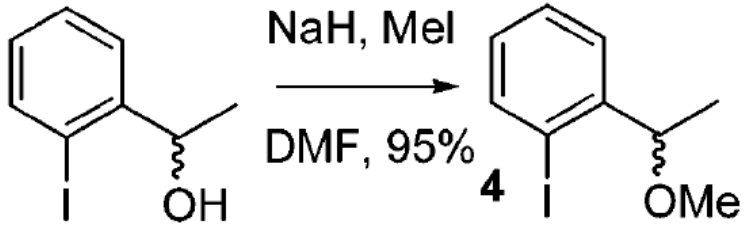
July 31, 2009

Normal Behavior of NaH



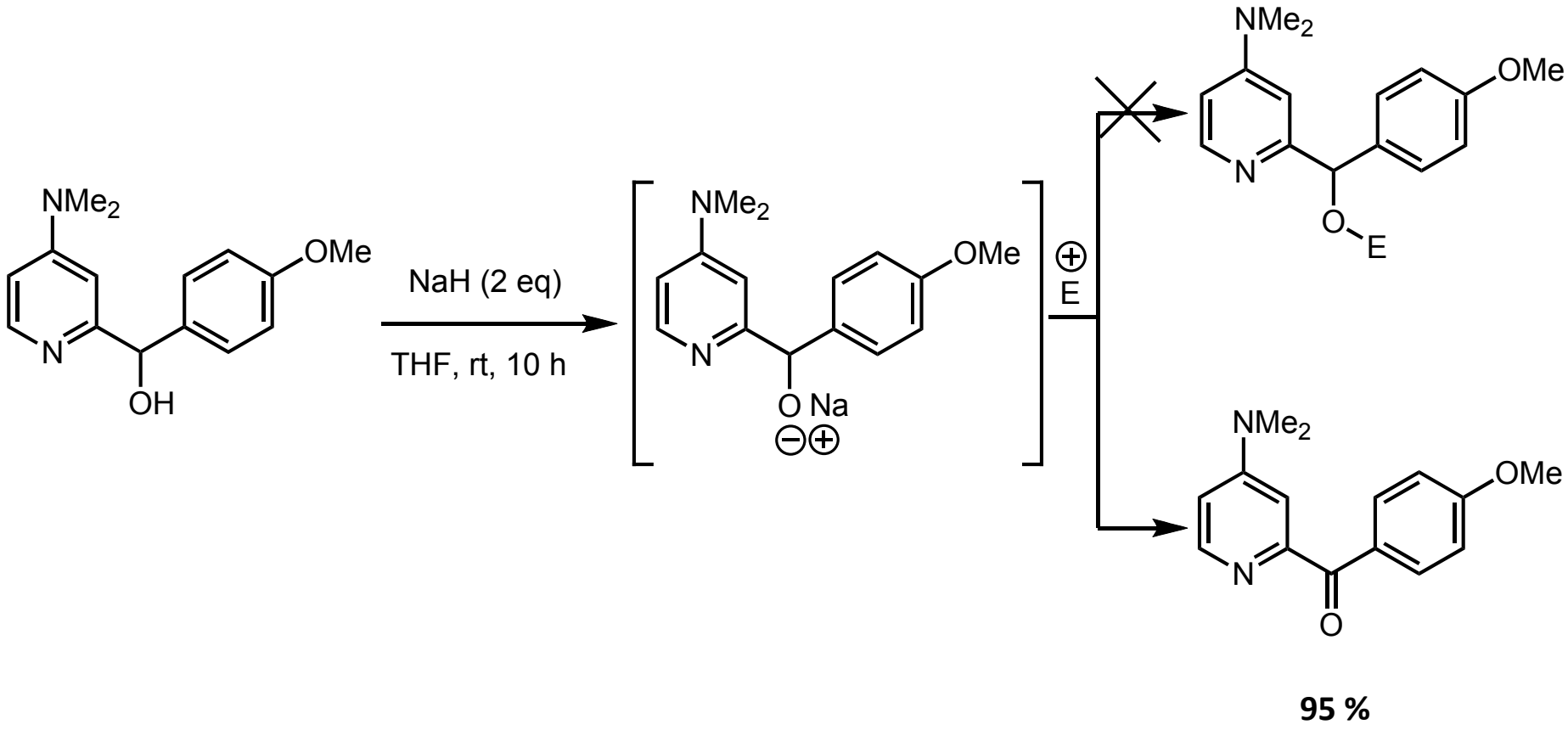
11 examples, 61–91%, dr 8:1–20:1

Morris, W. J.; Shair, M. D. *Org. Lett.* **2009**, *11*, 9.



Broutin, F-E.; Colobert, F. *Org. Lett.* **2005**, *7*, 3737-3740

NaH-Promoted Oxidation



95 %

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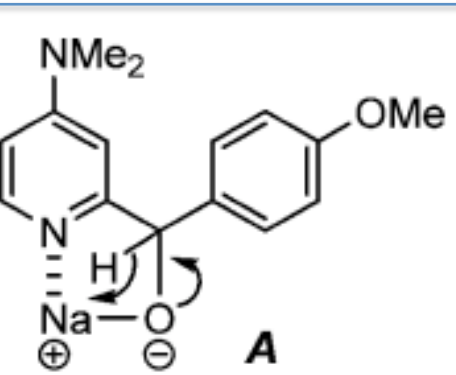
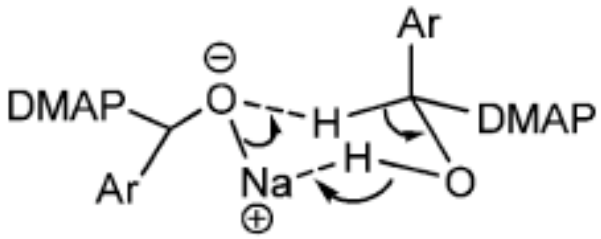
NaH-Promoted Oxidation: Proposed Mechanism



A



B

With electron withdrawing group	Retardation of the reaction rate	Enhancement of the reaction rate
Increase in the Concentration of the reaction	No Noticeable effect on the reaction rate	Substantial effect on the reaction rate

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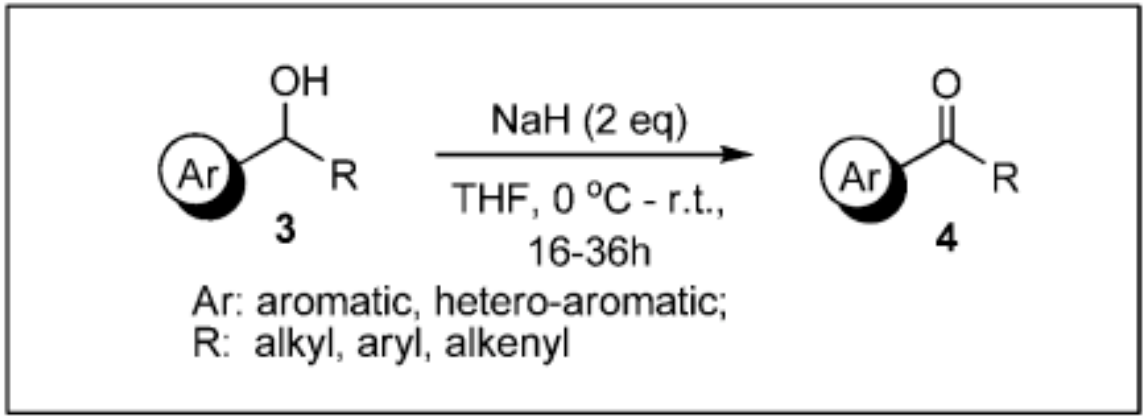
NaH-Promoted Oxidation: Reaction Conditions



Reagents	Na: Inactive NaOMe: Less efficient NaH: Most efficient	NaH = 2 equiv due to low solubility in THF
Solvents	THF DMF Toluene Ether	THF = Optimal Solvent (preliminary computational study suggest the coordination of THF to Na atom)
Concentration		0.2 M with respect to alcohol
Temperature		0 °C - rt

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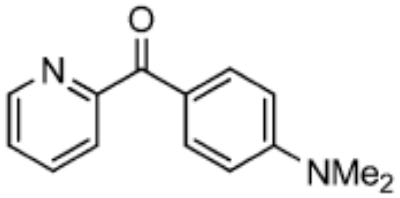
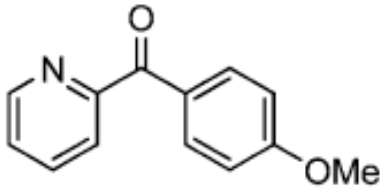
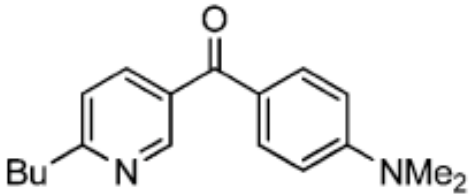
NaH-Promoted Oxidation: Substrate Scope



5: 99%

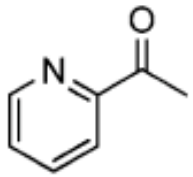


6: 94%

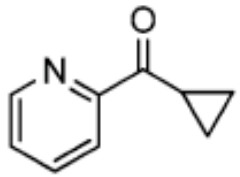


7: 88%

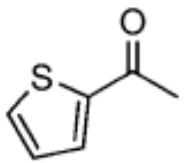
- Low yields for **11, 15**
- **5 g** scale of **5,6,7,8,13,14**
- **13, 14** in **83 %** and **88 %** using recovered NaH (2 eq.)



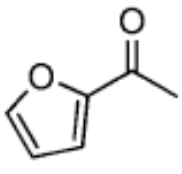
8: 76%



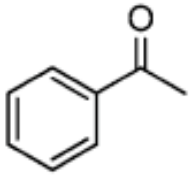
9: 81%



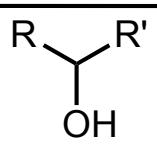
10: 99%



11: 24%

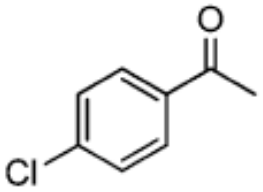


12: 59%
(75% by GC)

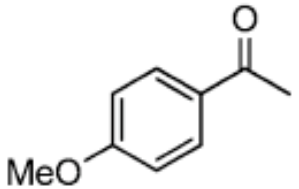


R = Alkyl, R' = Alkyl
R = Alkyl, R' = Propargyl
R = Propargyl, R' = Propargyl

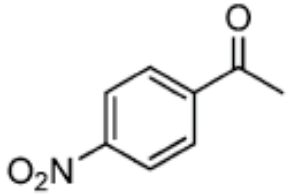
Reaction Failed !!



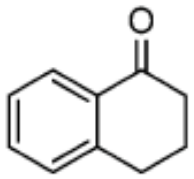
13: 85%



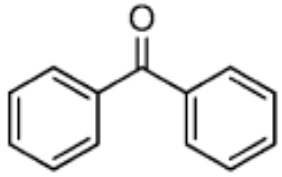
14: 87%



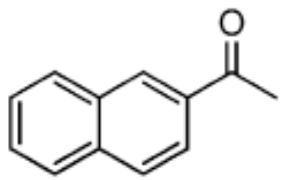
15: 12% (30h)



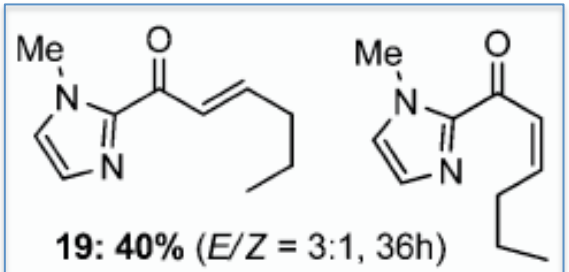
16: 53%



17: 90%



18: 62%



19: 40% (*E*/*Z* = 3:1, 36h)

A reversible hydride conjugate reduction event following the alcohol oxidation

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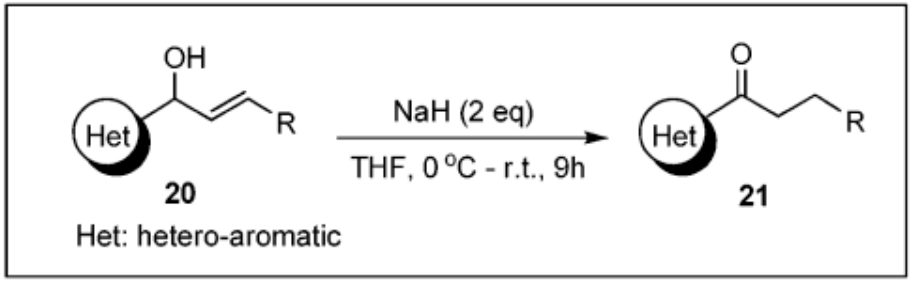
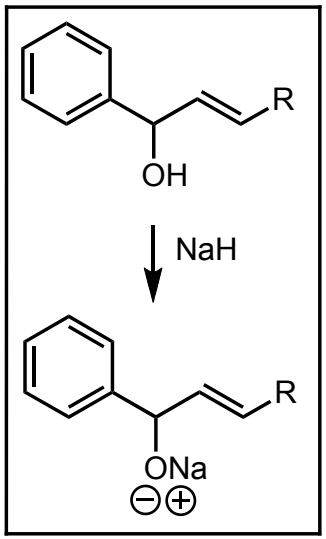
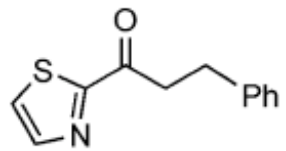
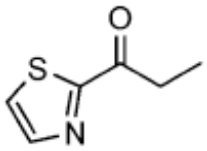
NaH-Promoted Tandem Alcohol Oxidation-Hydride Conjugative Reduction of Heterocyclic Allylic Alcohols



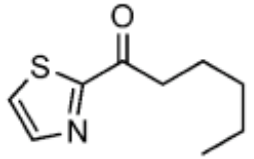




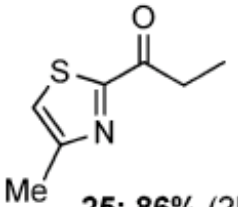
22: 54%



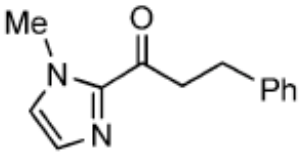
23: 64%



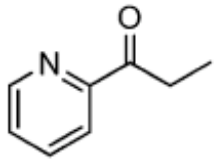
24: 68%



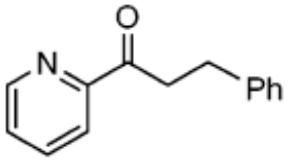
25: 86% (2h)



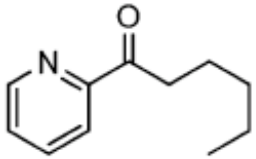
26: 68%



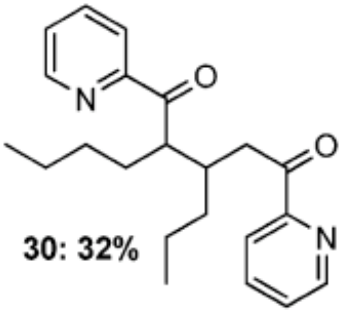
27: 68%



28: 30%



29: 50%



30: 32%

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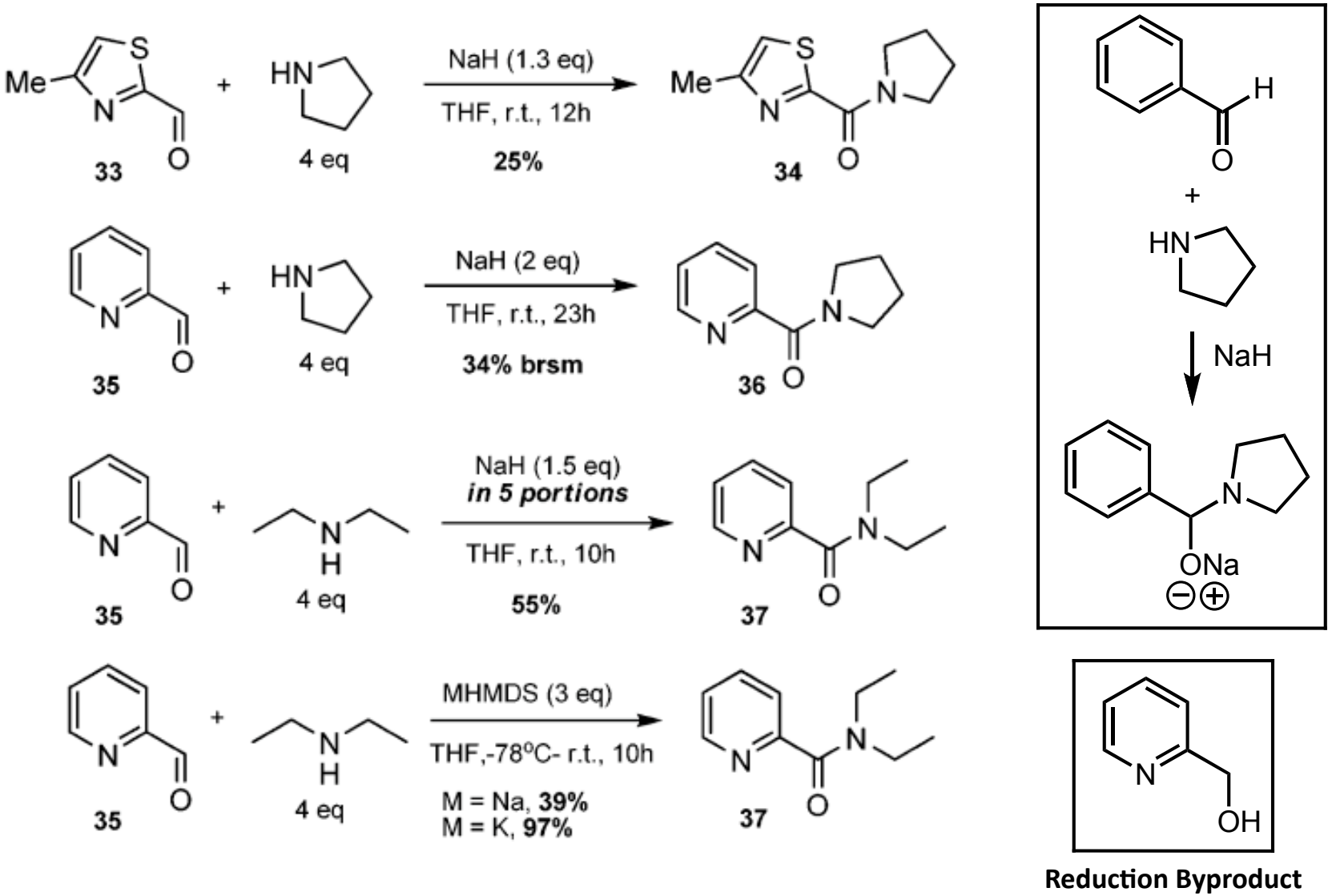
NaH-Promoted Oxidative Amidations of Some Heterocyclic Aldehydes



Wang, X.; Zhang, B.; Wang, D. Z. *J. Am. Chem. Soc.* **2009**, *ASAP*

Conclusion

- Unprecedented reactivities of NaH uncovered on:
  1. Alcohol oxidation
  2. Tandem allylic alcohol oxidation-hydride conjugate reduction
  3. Aldehyde oxidative amidation

- A significant level of material accessibility

- Operational simplicity

- Environmental compatibility (no metal residue or decomposition waste)

- NaH can be recovered and has the same reactivity

- Large scale reactions up to 5 g

- Could be used for economic preparation of pharmaceutically meaningful heterocyclic compounds

Wang, X.; Zhang, B.; Wang, D. Z. *J. Am. Chem. Soc.* **2009**, *ASAP*