

## Borrowing Hydrogen: Updates in Methodology

Reported by Noah Marcus

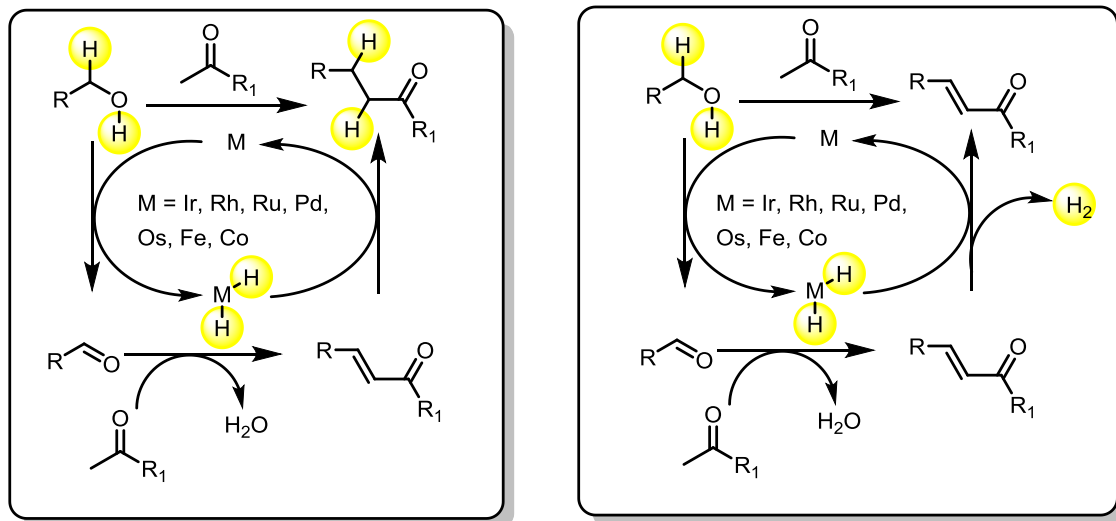
October 27<sup>th</sup> 2016

### Introduction

Borrowing hydrogen (BH) is the process where an alcohol is oxidized using a metal catalyst (usually Ru, Ir, Rh), the newly formed aldehyde is reacted with a nucleophile, an intermediate elimination event occurs resulting in an olefin which is subsequently hydrogenated by the metal-hydride present (Scheme 1). A similar process is termed acceptor-less BH or Semi-BH where the newly created olefin is not

reduced and H<sub>2</sub> is evolved instead (Scheme 1).

Hydrogen borrowing was first notably explored in 1981 by Grigg *et al.* in the synthesis of esters from

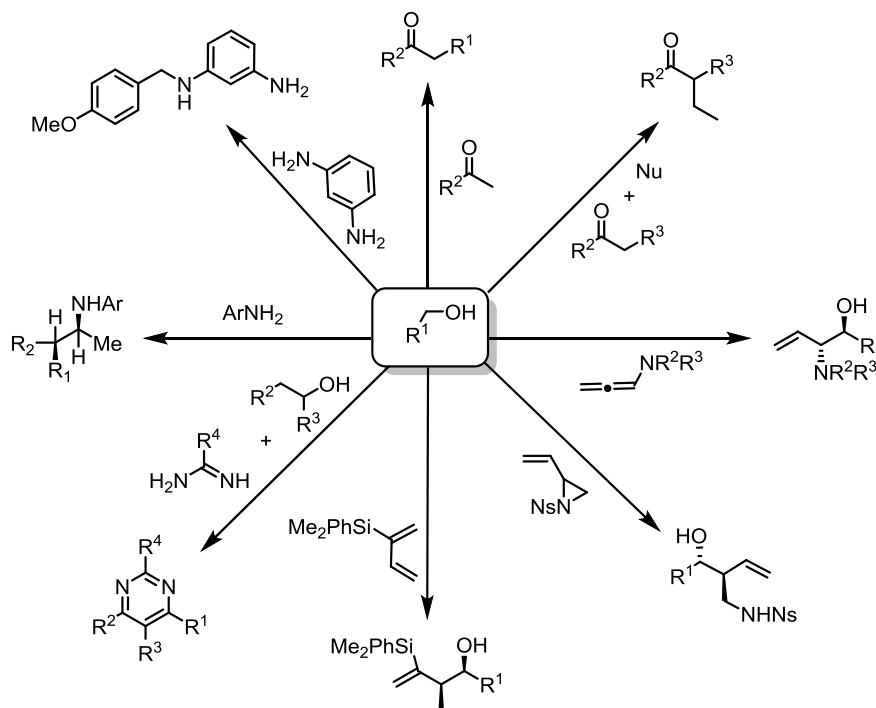


aldehydes and alcohols as well as N-alkylation of primary amines with alcohols.<sup>1,2</sup> In the years since Grigg's original findings and even in the past 5 years, many advancements have been made in BH methodology, catalysis and mechanistic understandings.<sup>3,4,5</sup>

### C-C bond formations:

In applying BH methods to C-C formations, tremendous effort has been put into expanding substrate scope (Scheme 2)<sup>3</sup>.

Alkylations of ketone via BH methods through an intermediate aldol condensation utilizing more stable and inexpensive alcohols as starting materials have been



extensively studied. Recently the Donohoe group has reported an interrupted BH process, allowing for addition of a nucleophile before olefin reduction, allowing for rapid diversification. Some of the greatest advances in C-C bond formations with BH technology has come in the form of diastereo- and enantioselective reactions, mainly reported by Krische. The generation of protected 1,2- and 1,3-aminoalcohols with high enantiomeric enrichment from achiral starting materials has been reported. Methods to perform highly diastereo- and enantioselective syn- and anti- selective crotylations of alcohols with 2-silyl-butenes and propargyl silyl-ethers was used. The use of propargyl chlorides has also been reported to form homo-propargyl alcohol.

### **C-N bond formations:**

Besides the C-C bond, the C-N bond is tremendously important in organic chemistry, especially in synthesis of biologically relevant molecules. In recent years the largest advancements in BH technologies for C-N bond formations have been catalyst designs, rapid formations of N-heterocycles as well as asymmetric bond formations.<sup>4,5</sup> New catalysts are continually being developed to perform alkylations of amines, amides and sulfonamides while being more cost efficient, less toxic, reusable and improving reaction conditions.<sup>5</sup> Recently the Kempe group reported a cobalt catalyst capable of singly alkylating diamines. The Shi group reported an all-carbon, heterogeneous catalyst capable of performing N-alkylation of amines as well as ketone alkylations in high yields. Recent advances in heterocycle formations have taken advantage of the acceptor-less BH variation. Kempe reported the multicomponent synthesis of di-, tri- and tetra-substituted pyrimidines in a region-selective fashion. Recent reports of BH-mediated kinetic dynamic asymmetric aminations as well as aminations with Ellman's sulfinamide have been recent advances in C-N bond formation setting stereogenic centers.

### **Future directions:**

While this field is continuing to grow and has a many strong researchers highly active many advances are still needed. Continued work similar on enantioselective BH reactions are important to the applicability of these methods. More attention to catalyst development needs to be put into C-C bond formation to allow these reactions to be more cost effective, less toxic and environmentally friendly.

### **References:**

- 1) Sutthivaiyakit, S; Mitchell, T. R. B.; Grigg, R.; *Tetrahedron*, **1981**, 37 (24), 4313-4319
- 2) Sutthivaiyakit, S; Mitchell, T. R. B.; Grigg, R.; *J. Chem. Soc. Chem. Comm.* **1981**, 611-612
- 3) Huang, F.; Liu, Z.; Yu, Z.; *Angew. Chem. Int. Ed.* **2016**, 55, 862-875
- 4) Yang, Q.; Wang, Q.; Yu, Z.; *Chem. Soc. Rev.* **2015**, 44, 2305
- 5) Shimizu, K.; *Catal. Sci. Technol.* **2015**, 5, 1412