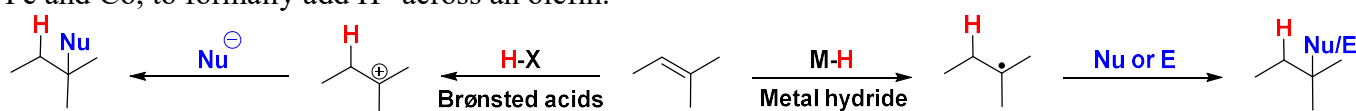


## Recent Advances in Base Metal-Catalyzed HAT Reactions with Unactivated Olefins

Tanner Bingham

03/27/18

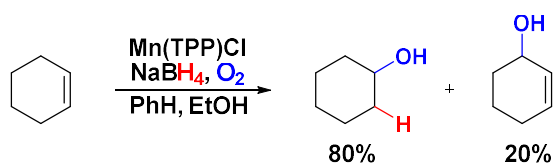
A Hydrogen Atom Transfer (HAT) is a fundamental chemical transformation that implies a concerted movement of a proton and an electron ( $H^\bullet$ ) from one group to another in a single step.<sup>1</sup> These types of reactions are ubiquitous throughout biology, playing roles in the mechanism of radical scavenging anti-oxidants,<sup>2</sup> as well as many enzymatic oxidations.<sup>3</sup> Organic chemists have been able to harness this mode of reactivity for over a century, to mediate many different chemical transformations such as C–H functionalization,<sup>4</sup> [1,*n*]-hydrogen transfer,<sup>5</sup> and radical dehalogenation.<sup>6</sup> More recently a new approach to this fundamental transformation has been developed using base metal hydrides with metals such as Mn, Fe and Co, to formally add  $H^\bullet$  across an olefin.



Scheme 1. Reactivity of Base Metal Hydrides versus Brønsted Acids

The addition of a  $H^\bullet$  places the resulting alkyl radical at the more substituted site of the olefin, thus exhibiting Markovnikov selectivity similar to what is observed in Brønsted acid-mediated olefin functionalization. While in some cases the same products can be formed through either reaction there are many benefits for taking a radical pathway. Compared to the harsh conditions required to form the carbocation intermediate in Brønsted acid-mediated hydrofunctionalization reactions, milder conditions can generally be employed to form the radical intermediate in base metal-catalyzed HAT reactions, resulting in higher chemoselectivity. Furthermore, radicals have an ambiphilic character and can act as either nucleophiles or electrophiles depending on their substituents, while carbocations can only act as electrophiles (Scheme 1). This allows for the selective tuning of reactivity for divergent functionalization.<sup>7</sup>

The base metal-catalyzed HAT reaction was first discovered in 1979 when Tabushi and Koga used  $Mn(TPP)Cl$  with  $NaBH_4$  and air as a model system for the enzymatic oxidation performed by the P-450 Fe-Heme system. Using cyclohexene as their substrate they found that the allylic oxidation occurred in 20% yield with concomitant formation of the hydrated product in 80% yield (Scheme 2). This result



Scheme 2. Seminal example of base metal catalyzed hydration

suggests that there is another pathway that is predominantly active in their system.<sup>8</sup> Other groups recognized the value in this new unexpected type of reactivity and expanded the use of metal sources to include Co and Fe. Furthermore, in 1989 Mukiyama showed that silyl hydrides act as more efficient reductants in these hydration reactions, providing synthetically useful yields at ambient temperatures.<sup>9</sup> These milder conditions lead to the wide spread use of the Mukiyama hydration in many total syntheses.<sup>7</sup> Since then, various groups have made

use of this mode of reactivity to develop other hydrofunctionalization processes, such as hydroperoxidation, hydroalkoxylation, hydronitrosolation, hydroazidation, hydrohydrazination, and hydroamination (Figure 1).<sup>7</sup>

In 1982, Okabe and Tada found that MeCo(dm<sub>g</sub>)<sub>2</sub>Py could perform reductive cyclizations between halides and olefins. Taking advantage of this precedent, van der Donk developed a reductive cyclization between two olefins using Ti citrate and Vitamin B12.<sup>10</sup> Further strategies to form C-C bonds were developed by Carreria, Baran and others. Carreria, elaborating on his hydroazidation, and hydrohydrazination, used TsCN to perform hydrocyanations.<sup>11</sup> Taking inspiration from the Geise reaction, in which nucleophilic alkyl radicals add into Michael acceptors, Baran developed a Fe-catalyzed reductive coupling of olefins and Michael acceptors, both intra and intermolecularly.<sup>12</sup> Since then, many groups have made progress in the field of reductive olefin coupling.<sup>7</sup>

Advances have also been made in the field of radical olefin hydrogenation. When base metal-catalyzed HAT reactions are conducted without the presence of an external radical trap the resulting alkyl radical could go through two main pathways, either hydrogenation or isomerization (Figure 2).<sup>7</sup>

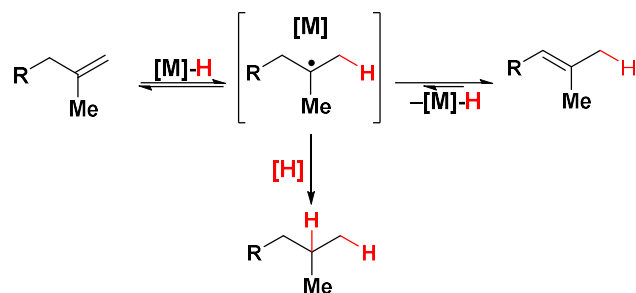


Figure 2. Hydrogenation versus isomerization pathway

Furthermore, Shenvi<sup>13</sup> and Norton<sup>16</sup> have reported conditions to effectively promote olefin isomerization that provides thermodynamically favored products.

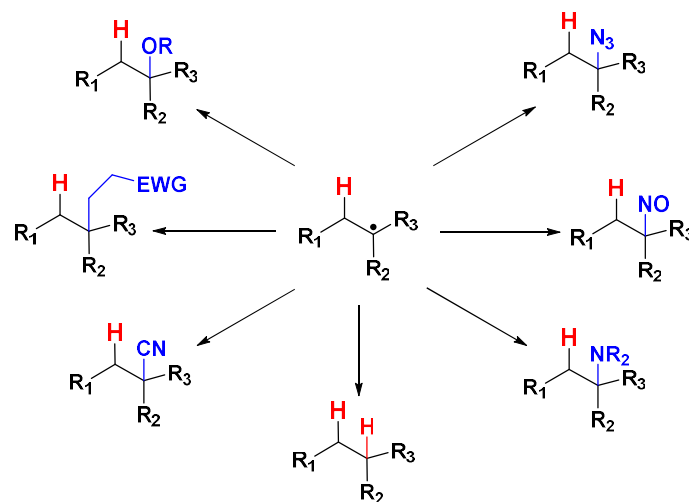


Figure 1. Divergent reactivity of alkyl radical intermediate

alkyl radical could go through two main pathways, either hydrogenation or isomerization (Figure 2).<sup>7</sup> Shenvi<sup>13</sup> and Herzon<sup>14</sup> have developed conditions selective for HAT-mediated hydrogenations that provide the thermodynamically preferred products, complementary to the kinetic selectivity seen for noble metal-catalyzed hydrogenation.

1. *J. Am. Chem. Soc.* **2007**, *129* 5153.
2. *Acc. Chem. Res.* **2015**, *48*, 966.
3. *J. Am. Chem. Soc.* **2002**, *124*, 8268.
4. *Nat. Chem.* **2015**, *7*, 987.
5. *J. Am. Chem. Soc.* **1960**, *82*, 1657.
6. *Acc. Chem. Res.* **1968**, *1*, 299.
7. *Chem. Rev.* **2016**, *116*, 8912.
8. *J. Am. Chem. Soc.* **1979**, *101*, 6456.

9. *Chem. Lett.* **1989**, *18*, 1071.
10. *J. Org. Chem.* **2002**, *67*, 837.
11. *Angew. Chem., Int. Ed.* **2007**, *46*, 4519.
12. *J. Am. Chem. Soc.* **2014**, *136*, 1304.
13. *J. Am. Chem. Soc.* **2014**, *136*, 1300.
14. *J. Am. Chem. Soc.* **2014**, *136*, 6884.
15. *J. Am. Chem. Soc.* **2014**, *136*, 16788.
16. *J. Am. Chem. Soc.* **2016**, *138*, 7698.