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Outlook

Borrowing Hydrogen for Organic Synthesis

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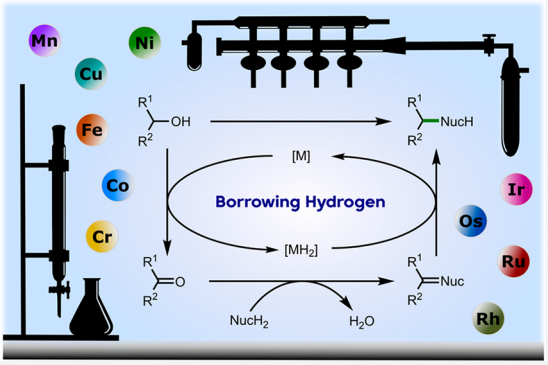
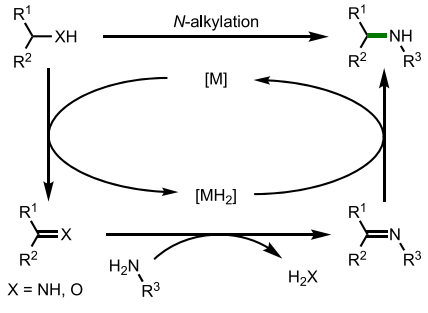
ABSTRACT: Borrowing hydrogen is a process that is used to diversify the synthetic utility of commodity alcohols. A catalyst first oxidizes an alcohol by removing hydrogen to form a reactive carbonyl compound. This intermediate can undergo a diverse range of subsequent transformations before the catalyst returns the "borrowed" hydrogen to liberate the product and regenerate the catalyst. In this way, alcohols may be used as alkylating agents whereby the sole byproduct of this one-pot reaction is water. In recent decades, significant advances have been made in this area, demonstrating many effective methods to access valuable products. This outlook highlights the diversity of metal and biocatalysts that are available for this approach, as well as the various transformations that can be performed, focusing on a selection of the most significant and recent advances. By succinctly describing and conveying the versatility of borrowing hydrogen chemistry, we anticipate its uptake will increase across a wider scientific audience, expanding opportunities for further development.



INTRODUCTION

Hydrogenation is a ubiquitous transformation in chemistry with an enormous range of uses, from the synthesis of fine chemicals to the production of common margarine.[1−3] An important subdivision of hydrogenation reactions is transfer hydrogenations, whereby hydrogen may be transferred from one molecule to another, rather than utilizing hydrogen gas.[4] Borrowing hydrogen chemistry, also known as hydrogen autotransfer, operates under this regime but with a key difference; in a borrowing hydrogen reaction, a pair of transfer hydrogenations is coupled with an intermediate reaction on the *in situ*-generated reactive intermediate.[5−9] The general pathway is shown (Scheme 1), as illustrated with amine N-alkylation.

Scheme 1. Generalized Transition-Metal-Catalyzed Borrowing Hydrogen Reaction



The process begins with a transition-metal mediated dehydrogenation of an alcohol or amine to form a reactive carbonyl (or imine) intermediate. This unsaturated species can undergo a variety of subsequent transformations, including condensation with an amine. The resulting species can be reduced by $[MH_2]$, generated in the initial dehydrogenation step, to regenerate the active catalyst and liberate the product of the reaction (in this case, an N-alkylated amine), to complete the catalytic cycle.

Most commonly, the borrowing hydrogen approach enables the functionalization of alcohols, with the vast majority of transformations utilizing commodity alcohols directly as alkylating agents in a variety of C−N and C−C bond-forming processes. This is an appealing strategy in comparison to alternative alkylation approaches. For example, commonly employed strategies for N-alkylation include alcohol activation (e.g., alkyl halide/sulfonate formation) and subsequent substitution or alcohol oxidation (to the corresponding carbonyl compound) followed by reductive amination. Both approaches are multistep and generate stoichiometric waste products. The borrowing hydrogen approach is typically selective for monoalkylation, providing complementarity to

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many traditional alkylation methodologies. Furthermore, through the use of chiral catalysts, enantioselective borrowing hydrogen reactions have been developed.

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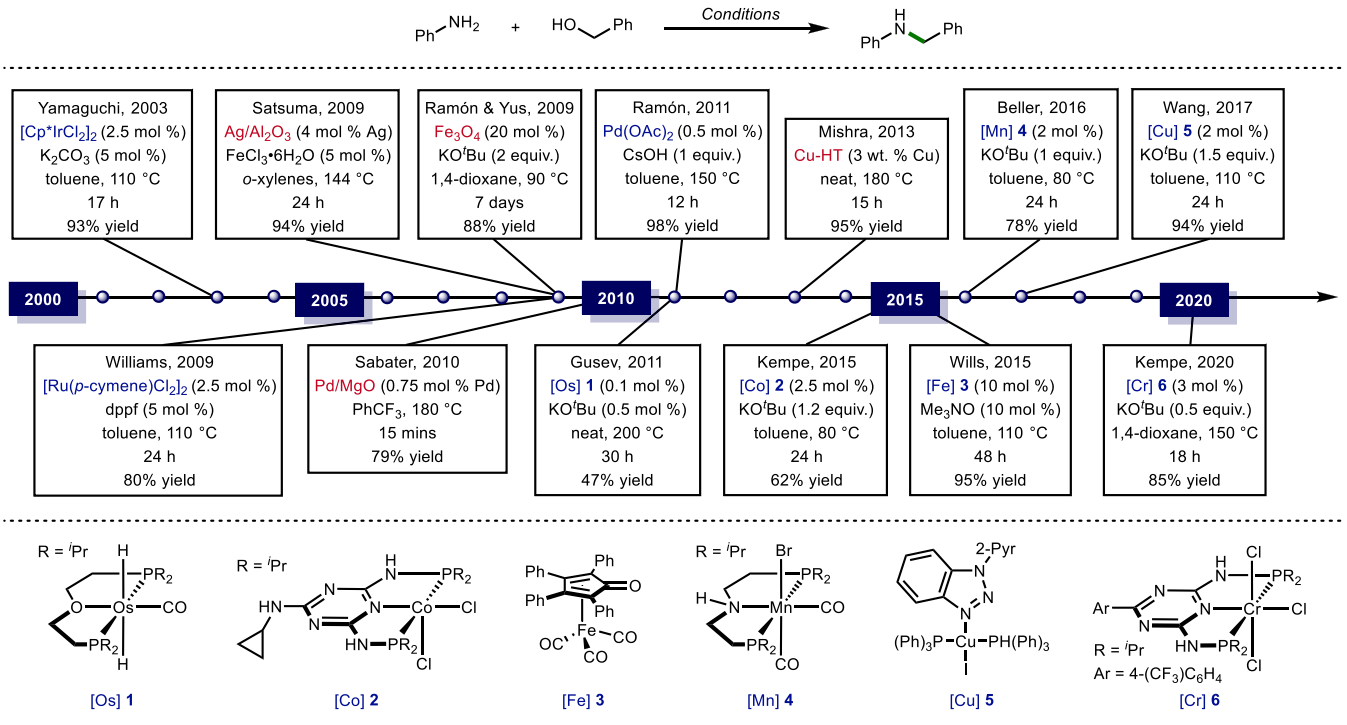
The term "borrowing hydrogen" was coined in 2004 by Williams and co-workers;[10] however, there are multiple examples of this approach being demonstrated decades earlier. An early example is the work of Winans and Adkins, who in 1932 reported the use of a supported nickel catalyst for the N-alkylation of anilines with alcohols.[11] Other examples employing heterogeneous catalysis followed in the ensuing years, such as a report by Pratt and Frazza, where an alternative nickel catalyst was used to achieve the same transformation.[12] By contrast, some of the earliest examples of homogeneous catalysis for borrowing hydrogen were not reported until the 1980s, when the works of Wantanabe and Grigg demonstrated the N-alkylation of anilines and acetonitrile derivatives with alcohols using ruthenium- and rhodium-based catalysts, respectively.[13−15] These pioneering contributions demonstrated the potential of this approach and inspired many research groups to investigate further, including our own.

This outlook provides a perspective on the borrowing hydrogen approach, primarily focusing on advances since 2000. It features landmark contributions, the different types of transformations that can be realized, and the diversity of catalytic manifolds that can be employed, spanning heterogeneous, homogeneous, and biocatalytic systems. We will highlight the current capabilities, limitations, and applications of these methodologies, direct specialists to further reading, and stimulate further interest and research in this exciting field. This outlook will not cover related base-mediated alkylation processes, which have been reviewed previously.[16]

C–N BOND-FORMING PROCESSES

N-Alkylation processes are a key facet of borrowing hydrogen chemistry, enabling alcohols (and amines) to be employed directly as alkylating agents in a diverse array of C–N bond-forming reactions with various N-nucleophiles. The formation of *N*-benzylaniline from aniline and benzyl alcohol is the archetypal borrowing hydrogen reaction of this class and has been widely explored, with a plethora of literature examples. An overview of selected metal catalysts that have been employed for this transformation, alongside the reaction conditions and reaction yield, is shown chronologically in Scheme 2. Heterogeneous and homogeneous catalyst systems are highlighted in red and blue, respectively. While earlier works date back to the 1930s,[11] the resurgence and subsequent popularity of borrowing hydrogen chemistry began in the early 2000s, where this outlook is focused. In 2003, Yamaguchi and co-workers utilized a homogeneous iridium-cyclopentadienyl complex in the N-benzylation of anilines—an excellent representative example.[17] Williams and co-workers employed a ruthenium *p*-cymene dichloride dimer to perform the same reaction in 2009.[18] The use of many alternative catalysts and reaction conditions was also reported in this year, with Satsuma[19] and Ramón and Yus[20] demonstrating the use of heterogeneous catalysts: supported silver and magnetite, respectively. Further studies showed the ability of many other metals to catalyze this transformation. In 2010, Sabater

Scheme 2. Selected Approaches for the Catalytic Synthesis of *N*-Benzylaniline via Borrowing Hydrogen



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and co-workers reported the synthesis of *N*-benzylamine via a heterogeneous palladium-catalyzed borrowing hydrogen process.[21] Other works utilizing gold catalysis also accomplished this transformation in the same year.[22] In 2011, Ramón and co-workers reported a homogeneous palladium-catalyzed borrowing hydrogen reaction, using palladium(II) acetate.[23] Gusev and co-workers reported an osmium-catalyzed borrowing hydrogen process utilizing an osmium PNP complex (**1**) in the same year,[24] followed by another report using tin catalysis.[25] In 2013, Kantam and co-workers reported a rhodium-catalyzed borrowing hydrogen formation of *N*-benzylaniline,[26] and Satsuma and co-workers demonstrated a heterogeneous nickel-catalyzed transformation to the same product.[27] Mishra and co-workers employed a heterogeneous copper catalyst immobilized on hydrotalcite (HT), further increasing the diversity of available catalysts for this transformation,[28] and in 2014, further reports of borrowing hydrogen transformations were disclosed, where rhenium catalysis was employed to perform this reaction.[29]

At this time, early examples of earth-abundant transition-metal catalysis in borrowing hydrogen reactions were reported, inspiring much further research in the use of 3d-block transition-metals in this area. The groups of Kempe[30] and Wills[31] reported the use of cobalt and iron catalysis for this transformation in 2015. Both systems employed well-defined metal complexes (**2** and **3**). Beller and co-workers increased the range of earth-abundant metal catalysts available in 2016, reporting a manganese-catalyzed reaction using a PNP-pincer precatalyst (**4**).[32] A year later, Banerjee and co-workers demonstrated the use of simple nickel(II) bromide as a precatalyst, using a phenanthroline ligand to create a homogeneous nickel catalyst.[33] Homogeneous copper-catalyzed borrowing hydrogen (**5**) can also be affected, as demonstrated by Wang and co-workers in 2017.[34] Most recently, Kempe and co-workers reported the use of a chromium PNP-pincer complex (**6**).[35]

The N-benzylation of aniline with benzyl alcohol is the archetypal C−N bond-forming borrowing hydrogen transformation. However, both the amine and alcohol can be varied extensively, encompassing a wide range of functional groups on both components. A selection of products that can be accessed from the methods described in Scheme 2 is shown in Figure 1, to highlight some of the functionalities that can be incorporated into products. Heterocyclic moieties are well tolerated, including the synthesis of *N*-benzyltryptamine (**7**), which also showcases the use of an alkyl amine nucleophile. Esters that could be susceptible to hydrogenation or amidation can also be tolerated in these processes (**11**). Product **12** shows good selectivity for the desired aniline being formed.[35] Furthermore, the presence of halides rarely impedes these reactions and can serve as functional handles for further elaboration.[36] These reactions typically show exquisite selectivity for mono-N-alkylation—an important distinction in the use of classical alkylating reagents, such as alkyl halides. The synthesis of compounds resembling active pharmaceutical ingredients (APIs), or the functionalization of biologically relevant molecules, has also been demonstrated. For example, Beller and co-workers reported the synthesis of molecules that bear structural resemblance to resveratrol (**14**),[37] which finds use in the treatment of Alzheimer's disease.[38]

Variations from aniline nucleophiles are possible and provide further breadth to this chemistry, as initially shown in Figure 1. For instance, aliphatic primary and secondary

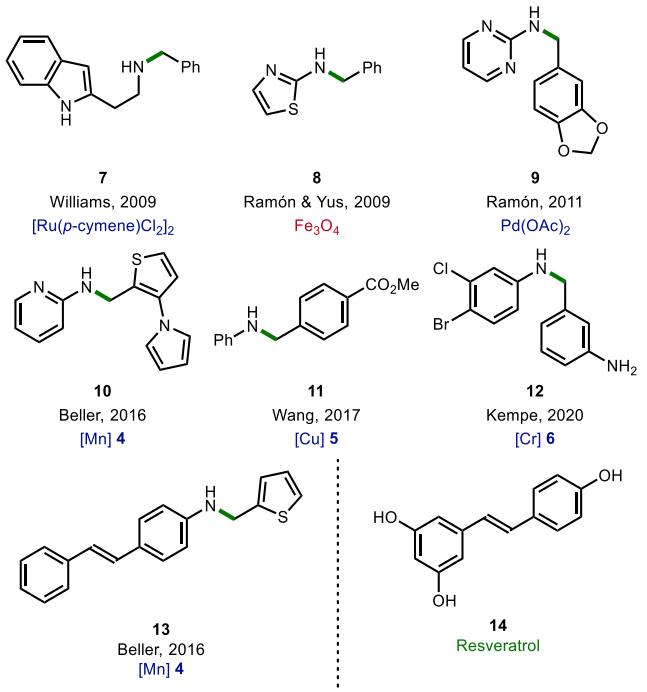

Figure 1. Examples showcasing product diversity.

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amines are shown as effective nucleophiles, with many literature reports.[39−45] An interesting example can be found in the work of Newton and co-workers of AstraZeneca.[46] The authors utilized ruthenium and iridium catalysis to provide alternative strategies in the synthesis of a variety of APIs. A range of compounds with piperazine moieties was synthesized on a multigram scale from primary and secondary amine nucleophiles. For example, key piperazine **16**, used to synthesize API **17**, was accessed in a one-pot fashion with a much simpler workup and impurity removal than the previous strategy (Scheme 3). This demonstrated the exciting opportunities for borrowing hydrogen in industry—in many cases, these reactions superseded the existing route by providing simpler workups or the avoidance of classical alkylating reagents. It is noteworthy that where aliphatic primary amines are employed, these reactions are often selective for the formation of tertiary amines, in contrast to the examples in Figure 1, where the formation of secondary anilines is most commonly observed.

Further variation of the N-nucleophile has expanded the array of transformations possible using borrowing hydrogen. For example, the N-alkylation of sulfonamides has been widely reported with primary alcohols.[47−49] Dong, Guan, and co-workers employed chiral nonracemic sulfinamides as nucleophiles in a diastereoselective N-alkylation with secondary alcohols, using Ru-Macho (**19**) as a borrowing hydrogen catalyst.[50] Representative examples and reaction conditions are

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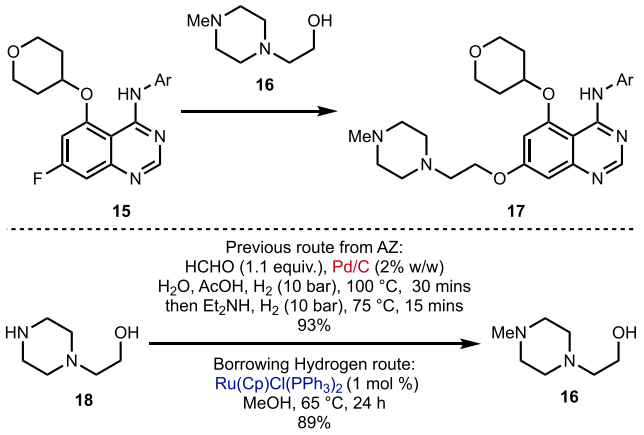
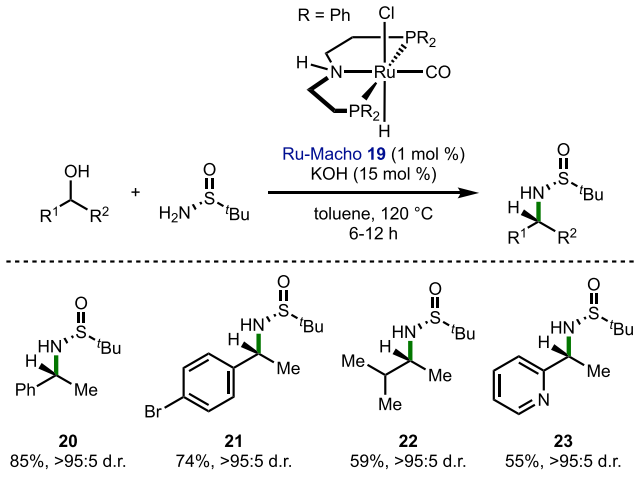
Scheme 3. Routes Toward API Synthesis with Borrowing Hydrogen



shown in Scheme 4, demonstrating excellent diastereocontrol across a range of substrates (**20**−**23**). A similar strategy was

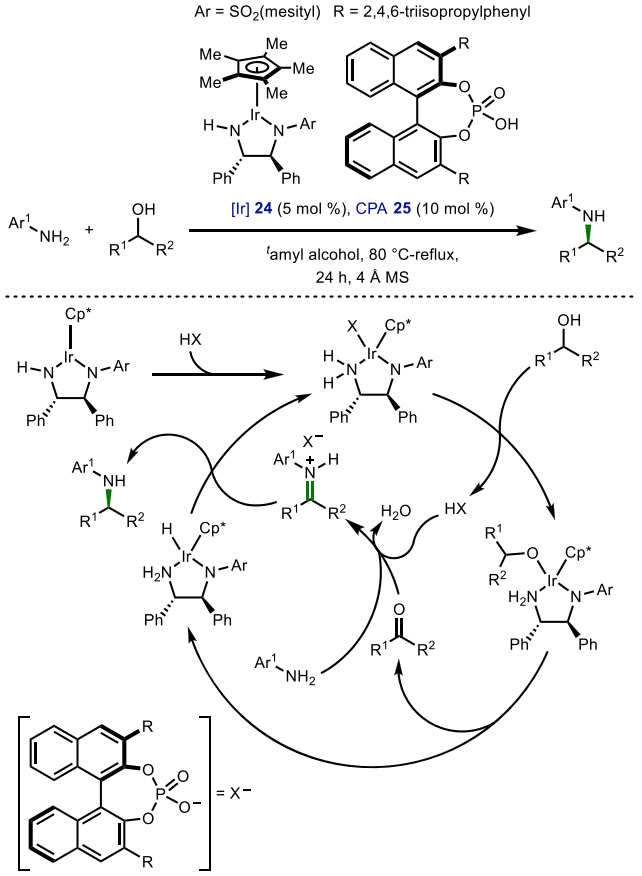
Scheme 4. Diastereoselective N-Alkylation of Sulfinamides



employed by Xia and co-workers, who used iridium catalysis to prepare two pharmaceutically relevant molecules.[51] An excellent example of the application of this work is the synthesis of (*S*)-rivastigmine, an acetylcholinesterase inhibitor used in the treatment of dementia.[52]

Multiple strategies for enantioselective N-alkylation have been explored within the field of borrowing hydrogen.[53−58] An excellent example was reported by Zhao and co-workers in 2014.[59] This reaction demonstrated the successful fusion of Brønsted acid organocatalysis with borrowing hydrogen catalysis—the combination of a chiral iridium catalyst (**24**) and a chiral phosphoric acid (CPA, **25**) was used in the preparation of enantioenriched *α*-branched amines. The reaction conditions, catalysts, and proposed mechanism are shown in Scheme 5. A wide range of alcohols was employed as alkylating reagents, with the resulting products reported in up to 97% e.e., despite the elevated reaction temperature. The authors attribute this enantioselectivity to both the chiral iridium catalyst and the coordination of the chiral phosphate anion. This approach was later extended to the dynamic kinetic resolution of racemic alcohols into enantioenriched amines[60]

Scheme 5. Enantioselective Alkylation of Amines



and to the enantioselective synthesis of tetralin- and indane-derived amines, as well as tetrahydroisoquinolines.[61,62]

An alternative strategy in the development of enantioselective borrowing hydrogen reactions is the use of biocatalysis, which has received much attention in recent years as a powerful technique for organic synthesis.[63,64] Early work of Kroutil and co-workers spearheaded investigations into the biocatalytic N-alkylation of amines with alcohols.[65] In general, an enzyme is used to oxidize secondary alcohols to ketones, and a second enzyme is used to perform a reductive amination of the ketone, returning the product amine. Often, a third enzyme is utilized to regenerate any required cosubstrates (such as adenosine triphosphate—ATP—or similar compounds) for either enzyme, thus allowing the catalytic cycle to continue. This was later reduced to two enzymes—an alcohol dehydrogenase and an amine dehydrogenase, an important advance reported by Turner and co-workers in 2015.[66] However, despite good enantiomeric excesses of the formed primary amines, these reactions were limited to aqueous ammonia as nucleophile, returning primary amines as products. Two years later, Turner and co-workers reported a significant advance: the tolerance of primary amines as nucleophiles.[67] Building on the earlier reported work, only two enzymes—an alcohol dehydrogenase and a reductive aminase (from the bacterium *Aspergillus oryzae*)—were required for this transformation. This design also allows for turnover of the cosubstrate required for the alcohol dehydrogenase (nicotinamide adenide dinucleotide phosphate, $NADP^+$) from the reductive aminase. Representative examples and a simplified catalytic cycle are illustrated in Scheme 6. The

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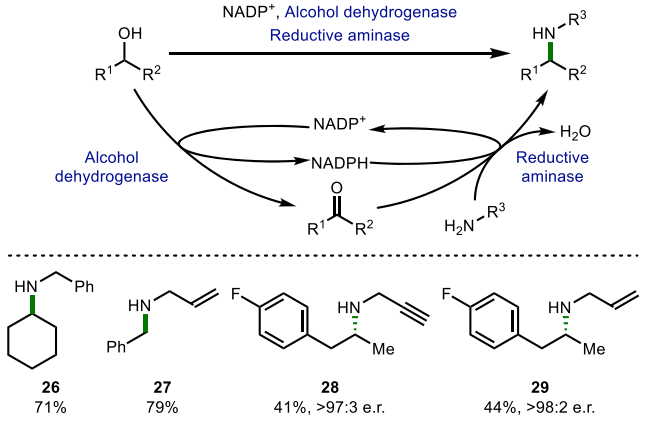
Scheme 6. Biocatalytic Borrowing Hydrogen with Primary Amines



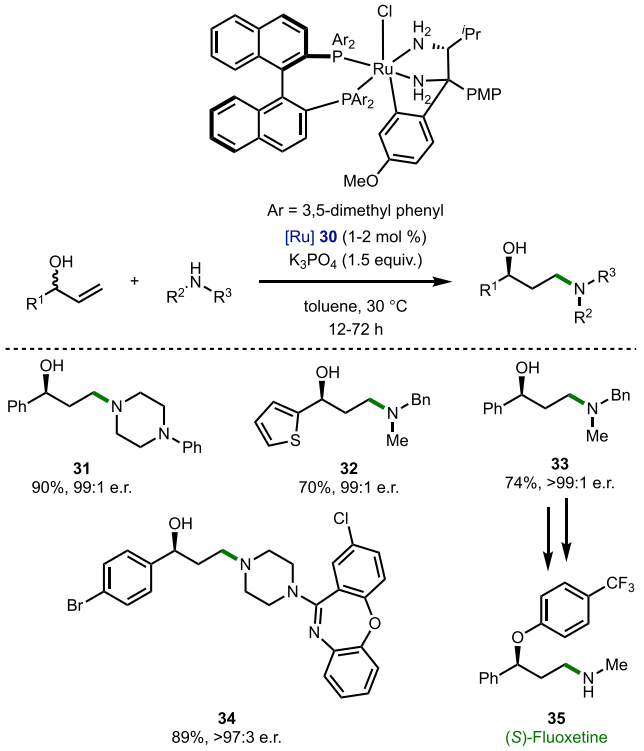
yields and enantiomeric excesses (where applicable) were high, exceeding 95% in many cases (**26**−**29**). Additionally, the low temperature of this reaction (only 30 °C) demonstrates the power of this biocatalytic system, alongside the range of transformations possible. A year later, an exciting extension of this work was published by Mutti and co-workers, who demonstrated a heterogeneous approach to biocatalysis by immobilizing the required enzymes on resin beads.[68] This allowed the authors to report this chemistry using nanomolar enzyme loading, with >99% enantiomeric excess in all examples.

Other variations in borrowing hydrogen N-alkylation chemistry come from employing alternative classes of electrophiles. For example, Sundararaju and co-workers reported the N-alkylation of amines with primary allylic alcohols.[69] This transformation has the additional challenge of competing 1,2- vs 1,4-addition of the amine nucleophile to the *in situ*-generated α,β-unsaturated carbonyl compound, in addition to possible isomerization of the allylic alcohol. However, the authors exclusively observed the formation of N-allylated products derived from the 1,2-addition of various primary and secondary amines. When propylamine was employed as the nucleophile, exclusive dialkylation was observed.

In the case of a 1,4-attack (γ-functionalization), the *anti*-Markovnikov hydroamination of secondary allylic alcohols has been reported employing ruthenium-[70] and iron-based catalysts.[71] More recently, a low temperature, stereoselective variant of this transformation was developed by Wang and co-workers, whereby a chiral ruthenium diamine-diphosphine complex (**30**) was employed to afford enantiomerically enriched γ-amino alcohols, bearing cyclic and acyclic tertiary amines (Scheme 7).[72] Very high enantiomeric excesses were observed in almost every case, with the authors reporting an impressive 94% average e.e. in over 60 examples. The authors highlighted that this method could be applied to the synthesis APIs commonly used in the treatment of depression, such as (*S*)-fluoxetine (**35**).[73] A similar ruthenium-catalyzed procedure for the γ-functionalization of allylic alcohols was reported shortly after by Xing and co-workers.[74]

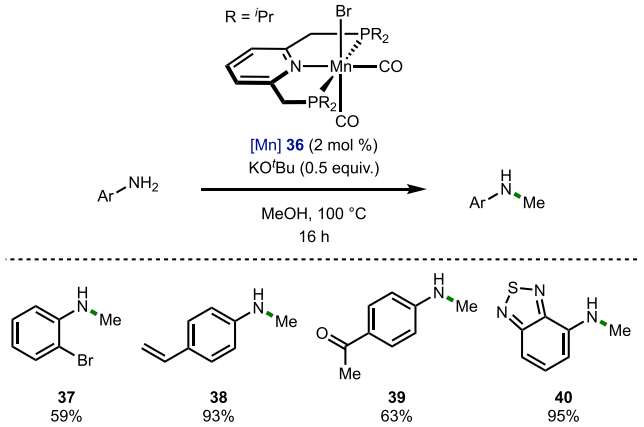
An important category of amine alkylation via borrowing hydrogen processes is methylations using methanol. These are challenging processes, partly due to the relatively high activation enthalpy of methanol dehydrogenation (ΔH = +84 kJ mol^{-1}), as compared to other longer chain aliphatic

Scheme 7. Enantioselective Hydroamination of Racemic Secondary Allylic Alcohols



alcohols, such as ethanol (ΔH = +68 kJ mol^{-1}).[75] An excellent example of borrowing hydrogen N-methylation procedures can be taken from the work of Beller and co-workers, who utilized a manganese PNP-pincer precatalyst (**36**) to effect selective mono-N-alkylation of anilines, tolerating a wide range of reducible functional groups (such as alkenes and ketones) and heterocycles. Scheme 8 shows the reaction conditions and

Scheme 8. Selective Mono-*N*-Methylation of Anilines



representative examples.[76] Other examples of methylation procedures include a range of precious and earth-abundant metal-catalyzed processes, reporting selective mono- or dimethylation of a variety of amines.[77−79] Additionally, the gas phase formation of methylamine from ammonia and methanol has been reported using various heterogeneous zeolite-based catalysts.[80,81] Further related reactions have been

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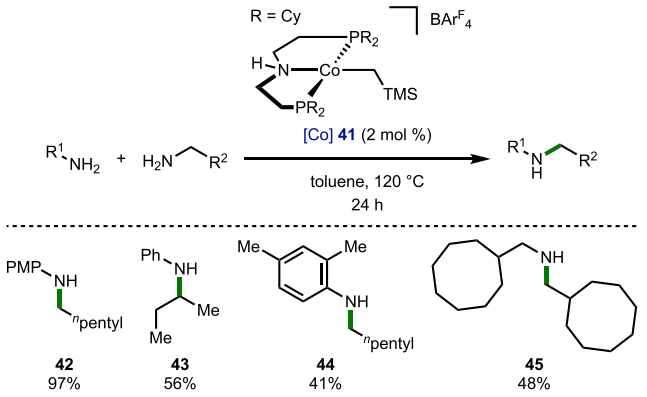
reported with the use of ethanol, as opposed to methanol.[40,44,82,83]

Another example of electrophile variation is the N-alkylation of amines using amines as alkylating agents: a formal amine cross-coupling. This reaction, by contrast with those that employ alcohols as the electrophile, produces ammonia as the byproduct. Early examples of this work include that of Williams and co-workers, who demonstrated the use of secondary and tertiary amines as alkylating reagents, such as diisopropylamine, using iridium catalysis.[84] Many other catalytic systems have also been reported for this process, predominantly using precious metal catalysts based on iridium, ruthenium, and platinum.[85−87] In 2016, Zheng and Zhang reported an earth-abundant transition-metal-catalyzed reaction of this class, utilizing a cobalt PNP complex (**41**).[88,89] A range of primary and secondary amines was employed as electrophiles. Interestingly, the nucleophilic amine was not limited to aromatic amines in this instance. A selection of amine homocouplings, from primary and secondary aliphatic amines, was also reported. Scheme 9 shows the reaction conditions,

Scheme 9. Amine Cross-Coupling Using Borrowing Hydrogen



catalyst structure, and representative examples. Park and co-workers also further explored amine cross coupling, utilizing a bimetallic cobalt/rhodium catalyst to synthesize secondary and tertiary amines.[89] This transformation has also been employed for the bulk production of secondary amines from primary amine feedstocks, using heterogeneous catalysis.[90−92]

C−C BOND-FORMING PROCESSES

At the same time as the research into N-alkylation was performed, many authors also focused upon C-alkylation processes using the borrowing hydrogen approach. This reaction, while related, is a distinct and powerful tool in the formation of new C−C bonds. The archetypal reaction used to showcase these developments is the formation of dihydrochalcone from acetophenone and benzyl alcohol. This reaction can also be performed with a wide range of metal catalysts, shown in Scheme 10. As for N-alkylation, there are early, pioneering examples of borrowing hydrogen-catalyzed C-alkylation processes;[13] however, this overview will focus on examples from 2000 and onward.

Early methods for this reaction utilized predominantly precious metal catalysts. For example, Chul Shim and co-workers employed a homogeneous ruthenium catalyst for the alkylation of acetophenones in 2002.[93] Subsequent work demonstrated various other transition-metal-catalyzed examples. A homogeneous iridium-catalyzed solvent-free process was devised by Ishii and co-workers in 2004,[94] while Cho and co-workers developed a heterogeneous palladium-catalyzed process soon after.[95] Both authors incorporated hydrogen acceptors (1-dodecene and 1-decene) in their respective processes to suppress further reduction of the ketone product to the corresponding alcohol. The need for such an additive was superseded as catalysts in other media became more selective for the reduction of the intermediates over the products. In 2007, Yus and co-workers utilized nickel in the form of nanoparticles (Ni NPs) to catalyze this reaction.[96] Investigations into new precious metal processes continued for several years, including reports of an osmium-catalyzed procedure from Yus and co-workers[97] and a heterogeneous hydrotalcite supported copper-catalyzed approach from Mishra and co-workers, both in 2013.[28] In the same year, Kantam and co-workers developed a rhodium-catalyzed procedure for alkylation of ketones with primary alcohols, albeit further reduction of the ketone products was observed.[26] Another strategy employing rhodium, this time able to obtain ketone products, was later realized by Wang and co-workers in 2016.[98] By this time, an increasing number of homogeneous earth-abundant transition-metal-catalyzed methods were emerging, including the works of Sortais and Darcel in 2015[99] and Beller and co-workers in 2016.[100] The former demonstrated the iron-catalyzed α-alkylation of ketones with primary alcohols, including application to a Friedländer-type annulation, to synthesize quinolines from 2-aminobenzyl alcohols. On the other hand, Beller and co-workers employed a manganese catalyst (**4**) to alkylate not only acetophenones but also oxindoles with primary alcohols. Beller and co-workers later utilized the same PNP-pincer ligand within a rhenium complex (**49**) to catalyze the C-alkylation of acetophenone using similar reaction conditions.[101] Soon after, a homogeneous cobalt-catalyzed process was reported in 2017 by Zhang.[102] Other related examples include a homogeneous nickel-catalyzed method, which was demonstrated by Banerjee and co-workers in 2018. In this case, the synthesis of dihydrochalcone was not explicitly achieved due to a tendency for dialkylation at the α-position of unbranched acetophenones under the reported conditions.[103]

A selection of examples from these publications demonstrates the excellent tolerance these processes have for a variety of functional groups, including heterocyclic moieties (Figure 2). Likewise, they exemplify the potential applications of the method to the direct synthesis or late-stage modification of natural products, such as the synthesis of donepezil (**56**) and the alkylation of an estrone derivative (**53**). C-Alkylation via the borrowing hydrogen pathway is not limited to the alkylation of methyl ketones but also is available to a variety of other nucleophiles. Nitrile compounds are a strategically useful building block in organic synthesis,[104] thus they are among the earliest[13] and most explored nucleophiles for C-alkylation using precious metal catalysis,[105,106] biocatalysis,[107] and, more recently, earth-abundant metal catalysis.[108−110] Similarly, functionalizing the α-position of esters and amides is possible but more challenging compared to the α-alkylation of ketones; the C−H acidity of esters and amides is comparably lower than ketones and aldehydes, while esters are also prone to undergo transesterification with alcohols. Early progress for the catalyzed α-alkylation of unactivated esters and amides with primary alcohols was made by Huang and Ishii, who both

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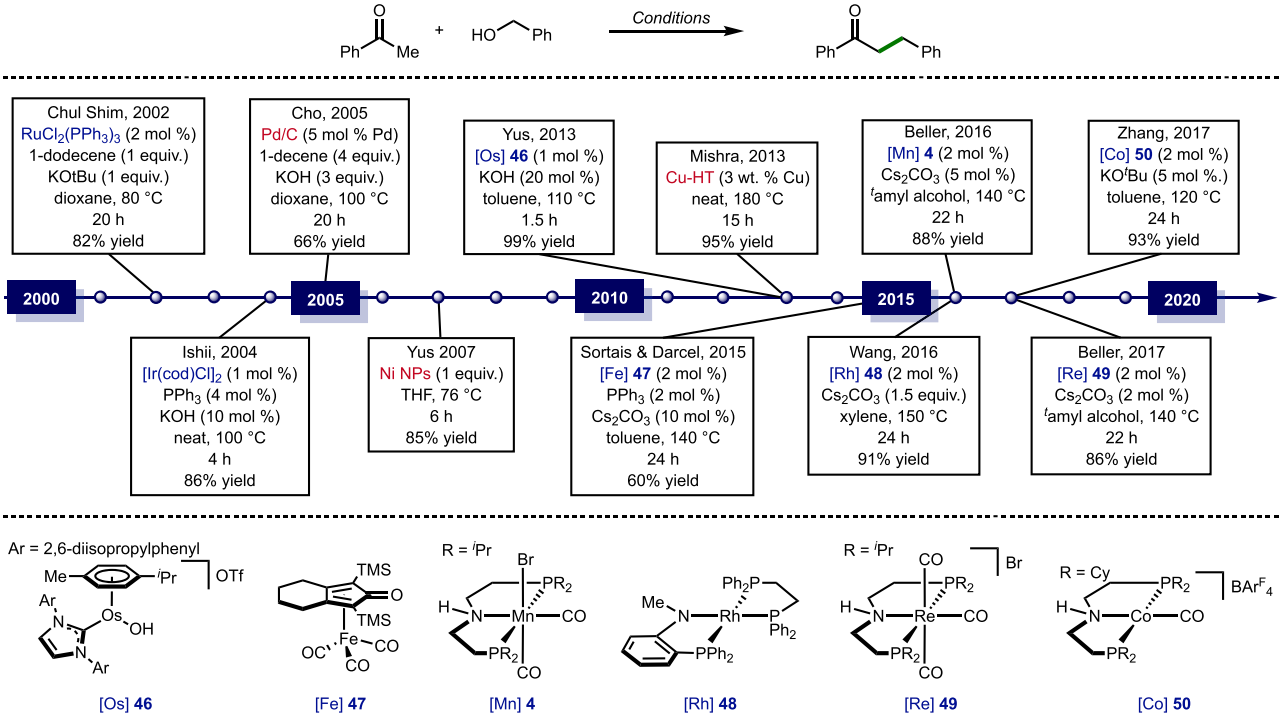
Scheme 10. Selected Approaches for the Catalytic Synthesis of Dihydrochalcone via Borrowing Hydrogen



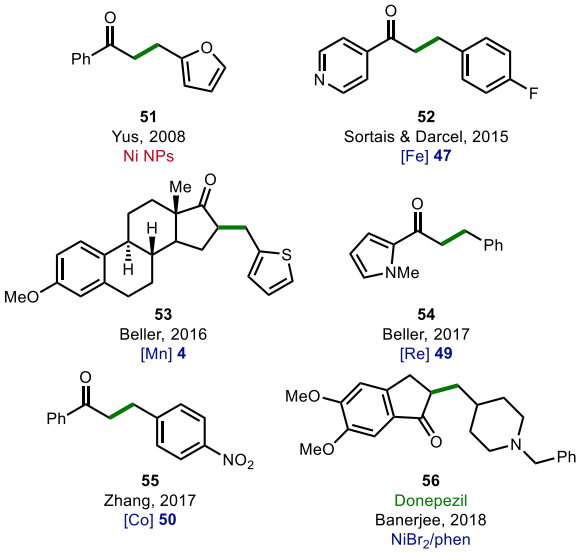
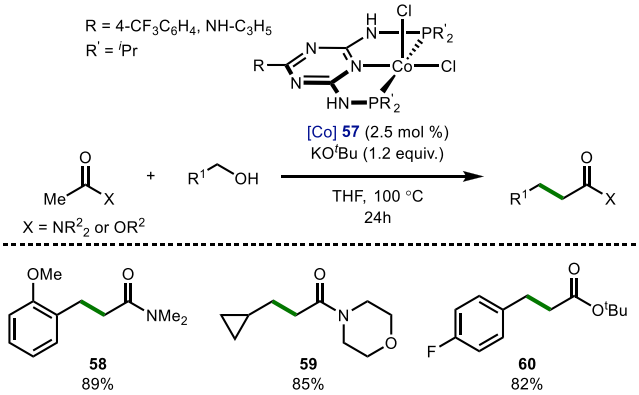


Figure 2. Functional group tolerance and natural product modification in the α-alkylation of ketones.

Scheme 11. α-Alkylation of Esters and Amides



developed iridium-catalyzed processes.[111−113] In 2016, Kempe reported the first earth-abundant metal-catalyzed α-alkylation of unactivated esters and amides using alcohols, via borrowing hydrogen. This reaction employed a homogeneous cobalt complex (**57**), shown along with representative examples (**58**−**60**) in Scheme 11.[114] This chemistry was extended to manganese[115,116] and nickel[117] catalysis. Other C-nucleophiles include indoles,[118,119] oxindoles,[100,120] heteroarenes,[121−123] napthols,[124] sulfones,[125] and thioamides,[126] which can be functionalized in similar ways.

Early C-alkylation works focused principally on the use of primary alcohols as alkylating agents, as the use of secondary alcohols was significantly more challenging.[127] This was partly due to the issue of competing self-condensation of both the substrate and the ketone intermediate derived from the secondary alcohol. A major breakthrough was made by Donohoe and co-workers in 2017, whereby they addressed the self-condensation issue by employing a pentamethylphenyl group (Ph*) to sterically shield the carbonyl of the starting material (1-(pentamethylphenyl)ethan-1-one) from attack by enolates formed *in situ*.[128,129] The Ph* group could be cleaved after workup by means of a retro-Friedel−Crafts acylation, to provide a series of β-branched esters and amides. Donohoe and co-workers also applied this methodology to the synthesis of (±)-3-methyl-5-phenylpentanol (**63**), a common fragrance additive used in cosmetics and toiletries.[130] Scheme 12 shows the reaction conditions for the borrowing hydrogen procedure and the subsequent retro-Friedel−Crafts reaction, with representative examples.[128] In recent years, this approach with secondary alcohols has been extended to cobalt,[131] iron,[132] manganese,[133] and transition-metal-free catalysis.[134]

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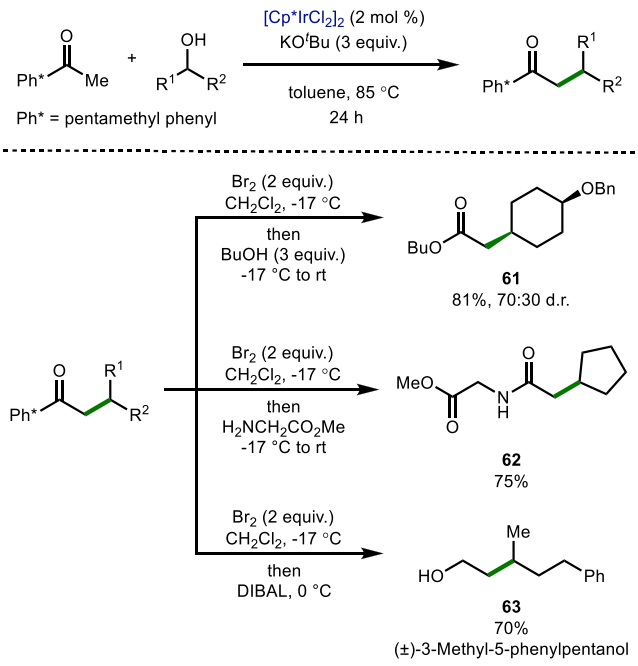
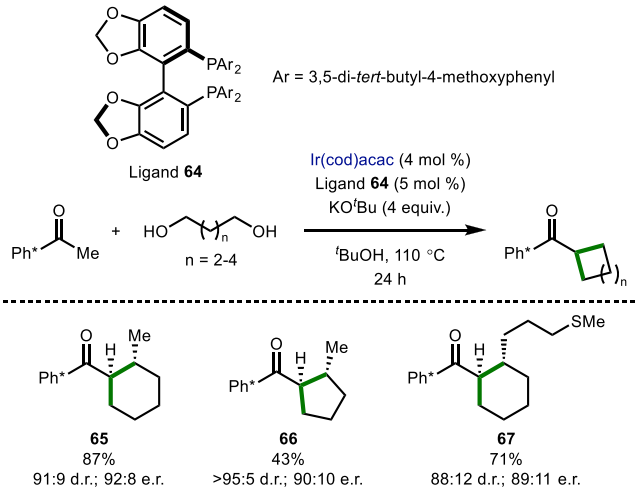
Scheme 12. α-Alkylation of Ketones with Secondary Alcohols, with Second Stage Derivatization of Products



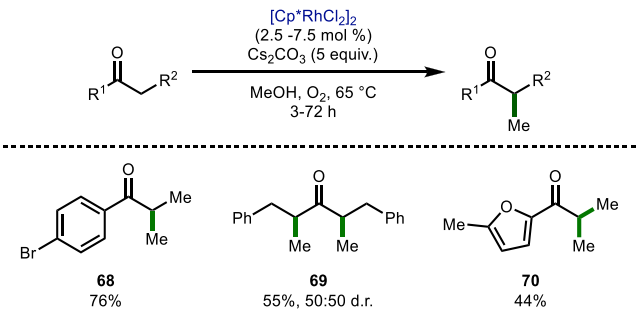
The Ph* group was also used in an iridium-catalyzed (5 + 1) annulation strategy to synthesize cyclohexanes using 1,5-diols as alkylating agents by the same authors.[135] It also was later incorporated for further stereoselective studies, utilizing a chiral phosphine ligand to control the facial selectivity of hydride deposition to the enone intermediate, resulting in enantioenriched products as shown in Scheme 13 (**65**–**67**).[136,137] The diastereoselective dialkylation of methyl ketones using diols to obtain cycloalkanes has also been performed with manganese[138,139] and iron catalysis.[140] A recent study from Gunanathan and co-workers successfully demonstrated the alkylation of unsubstituted and unhindered acetophenone compounds with secondary alcohols by employing Ru-Macho as the catalyst and, contrary to previous reports, using a catalytic amount of base.[141]

Scheme 13. α-Alkylation of Ketones with Diols



The research discussed so far is predominantly limited to methyl ketone substrates using benzyl or long chain *n*-alkyl alcohols as alkylating agents. The ability to perform methylation to form α-branched products via the borrowing hydrogen method remained a challenge for many years due to the same reasons discussed earlier for N-methylation.[76] In 2014, Donohoe made a breakthrough using a rhodium catalyst, while utilizing methanol as both the methyl source and the solvent.[142] This work also showcased double α-methylation of simple methyl ketones: a limitation in the interest of monoselectivity. Reaction conditions and representative examples are shown in Scheme 14. α-Methylation procedures were later established with earth-abundant metal catalysts, containing cobalt,[143] iron,[144] and manganese.[145,146]

Scheme 14. α-Methylation of Ketones



While the works described thus far have focused on the alkylation of ketones, the formal alkylation of alcohols is also possible via borrowing hydrogen catalysis. The β-alkylation of secondary alcohols with alcohols (alcohol cross-coupling) is much like the alkylation of methyl ketones, except an additional transfer hydrogenation sequence is required to generate a nucleophilic species and return an alcohol product. As a result, many of the catalysts discussed in Scheme 10 are capable of both transformations; therefore, several one-pot alcohol cross-coupling procedures have been accomplished throughout the borrowing hydrogen era, employing a range of metals under both homogeneous and heterogeneous catalysis.[147−155] Other notable reports showcasing β-alkylation of secondary alcohols include transformations related to those already discussed, stereoselective cycloalkane synthesis with diols,[139] and methylation. The β-methylation of secondary alcohols has been accomplished using heterogeneous iridium[156] and palladium catalysis,[157] as well as homogeneous ruthenium,[158] iron,[159,160] and, most recently, manganese catalysis.[161,162]

Recently, Zhao and co-workers demonstrated a significant improvement for alcohol β-alkylation—the iridium-catalyzed β-alkylation of secondary alcohols with primary alcohols at room temperature.[163] This was a remarkable feat, given the high temperatures typically required for borrowing hydrogen reactions. 3-Pentanone is used as a hydrogen acceptor to promote the reaction. The authors went on to report an enantioselective ruthenium-catalyzed alkylation of secondary alcohols with primary alcohols, obtaining enantiomeric excesses as high as 92%. Very few enantioselective reports with respect to C−C bond formation via a borrowing hydrogen cycle had been disclosed prior to this work.[164−166] Almost simultaneously, Wang and co-workers reported a closely related process, also employing a chiral ruthenium

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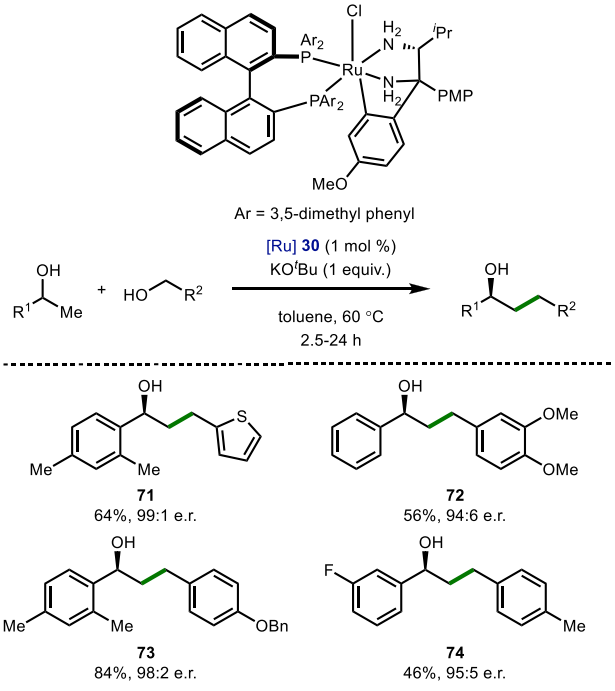
complex as the catalyst (**30**).[167] While this process occurred at 60 °C, there was no requirement for a promotor. A large number of examples were shown with products formed in up to 98% e.e., such as those highlighted in Scheme 15.

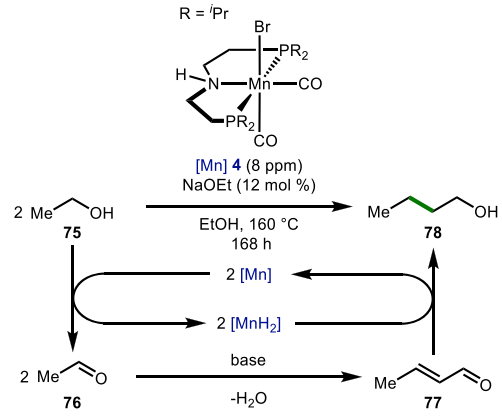
Scheme 15. Enantioselective *β*-Alkylation of Alcohols



There are other applications of the alkylation of alcohols, beyond the shown examples. As the world seeks to replace fossil fuels with more sustainable alternatives, alcohol-based fuels have emerged as a viable option.[168,169] *n*-Butanol as a biofuel has advantages over bioethanol, namely its higher energy density.[170] However, its main source of production is as a byproduct from the Acetone-Ethanol-Butanol (ABE) fermentation of biomass, a lengthy, inefficient process.[171] An alternative chemical pathway to *n*-butanol is the homocoupling of lower alcohols, a method which has been established for over a century since the original Guerbet reaction—which featured the coupling of aliphatic n-butanol to form 2-ethylhexanol.[172,173] Classically, this method requires an alkali metal hydroxide and Raney-nickel as a hydrogen transfer catalyst. Recent efforts have sought to apply other catalysts for the Guerbet reaction, with much interest surrounding the production of n-butanol via the homocoupling of ethanol. The vast majority of these processes employs a precious metal catalyst and requires high reaction temperatures (≤110 °C).[174−178] The first example of upgrading ethanol into higher alcohols using a homogeneous nonprecious metal catalyst was reported by Liu and co-workers in 2017.[179] Utilizing ppm levels of a PNP-pincer precatalyst (**4**) (8 ppm), they were able to achieve a very high TON (114,120), surpassing many precious metal-catalyzed examples, while also maintaining good selectivity for 1-butanol (92%), albeit still requiring high temperatures. Reaction conditions and a catalytic cycle are shown in Scheme 16.

As previously discussed in C−N bond-forming reactions, there is much potential in borrowing hydrogen chemistry for powerful, dual-catalytic systems. In 2013, Quintard and

Scheme 16. Upgrading of Ethanol to n-Butanol



Rodriguez combined an iron-catalyzed borrowing hydrogen cycle with secondary amine organocatalysis.[165] The authors were able to perform asymmetric *γ*-functionalization of simple allylic alcohols to obtain *γ*-functionalized alcohols using mild reaction conditions. The mechanism of this reaction is shown in Scheme 17. The reaction begins with catalyst activation with Me_3NO. The typical borrowing hydrogen reaction then occurs, but the intermediate enal can be intercepted by the secondary amine organocatalyst (**79**), resulting in an enantioselective Michael addition of the nucleophile (a *β*-keto ester, in this case) to the formed iminium ion. This is followed by hydrolysis and chemoselective reduction, regenerating the active iron dehydrogenation complex and generating the *γ*-functionalized alcohol product. The authors later extended this reaction to a one-pot synthesis of enantioenriched spiro-*δ*-lactones.[166]

In 2019, Dydio and co-workers combined borrowing hydrogen reactions with transition-metal-catalyzed functionalization to devise one-pot dual-catalytic systems.[180] One system combined a ruthenium-catalyzed borrowing hydrogen process with palladium-catalyzed arylation to generate *β*-aryl alcohols from primary alcohol substrates. A second transformation combined a borrowing hydrogen process with rhodium-catalyzed hydroarylation, ultimately to access enantioenriched *γ*-aryl alcohol products from primary allylic alcohols. In this study, both ruthenium and iron complexes were explored as a hydrogen transfer catalyst. Scheme 18 shows the reaction conditions and representative examples (**80**−**83**) when employing an iron complex (**47**) as a hydrogen transfer catalyst.

The coupling of olefins with alcohols via hydrogen autotransfer is a transformation demonstrated by many in recent years, as summarized in a review by Kirsche and co-workers.[181] They themselves have demonstrated ruthenium-catalyzed redox coupling of *α*-hydroxyesters and dienes. Using $Ru_3(CO)_{12}/PCy_3$ as a catalyst system, *α*-hydroxyester (**84**), and an excess of isoprene as olefin,[182] the postulated mechanism proceeds via oxidative coupling of isoprene (**85**) and the *in situ* generated ketone (**87**), as illustrated in Scheme 19. The resulting five-membered ruthenium(II) oxametallacycle (**88**) isomerizes to the seven-membered variant (**89**), followed by protonation of the oxametallocycle forming the ruthenium(II) alkoxide species (**90**). Subsequent *β*-hydride elimination to the ruthenium(II) hydride species (**91**), followed by reductive elimination, delivers the product (**86**) and a ruthenium (0) species, completing the catalytic cycle.

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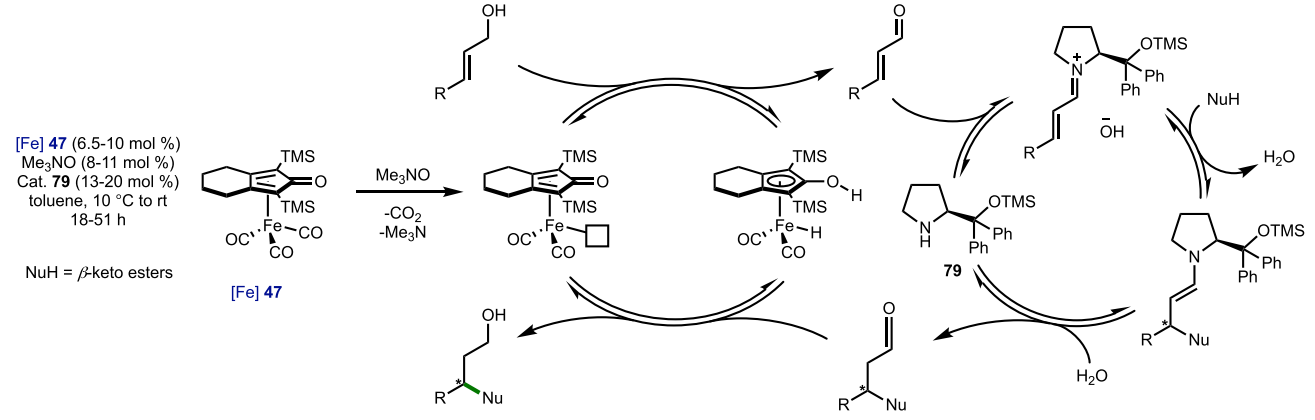
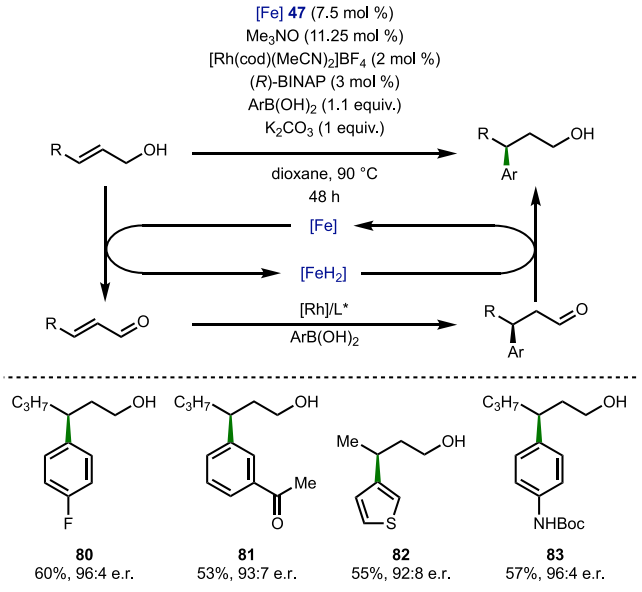
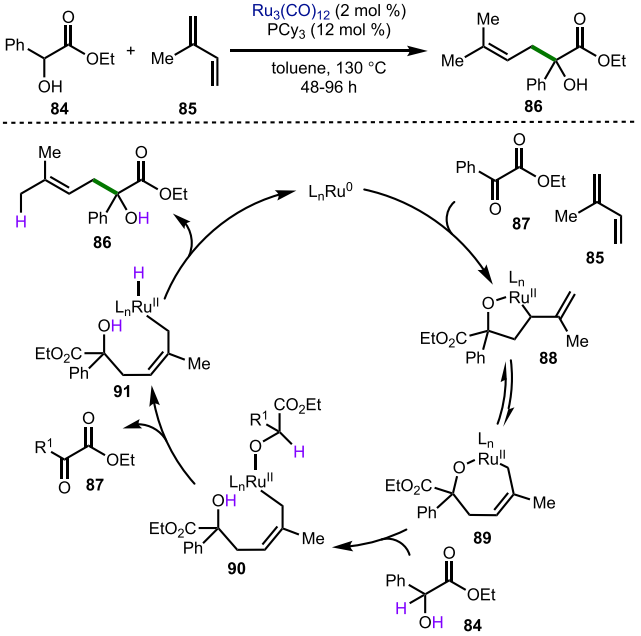
Scheme 17. Dual-Catalytic System Combining Borrowing Hydrogen Activation and Enantioselective Organocatalysis



Scheme 18. Dual-Catalytic Transition-Metal System to Access Enantioenriched γ-Aryl Alcohols from Allylic Alcohols



Scheme 19. Ruthenium-Catalyzed Redox Coupling of α-Hydroxyesters and Dienes



Similar ruthenium-catalyzed coupling processes from Krische and co-workers have been applied to heteroaryl substituted secondary alcohols,[183] as well as 3-hydroxy-2-indoles.[184]

MISCELLANEOUS PROCESSES

Almost all borrowing hydrogen works involve the formation of new C−C or C−N bonds. However, there are other useful applications of this methodology.[185] Deuterium labeled compounds are useful as internal standards for mass spectrometry, as solvents for NMR spectroscopy, and in medicinal chemistry for clarifying biosynthetic pathways.[186] In 2018, Prakesh and co-workers reported an effective strategy for the regioselective deuteration of primary alcohols.[187] An iron catalyst could selectively deuterate the α-position, while a manganese catalyst was able to deuterate at both the α- and β-positions. The postulated mechanism of the manganese-catalyzed transformation is shown in Scheme 20.

SUMMARY AND PERSPECTIVE

Within this outlook, we have provided an overview of the borrowing hydrogen approach and its application in synthesis. We have discussed the most significant advances across a variety of important C−N and C−C bond-forming processes. Several landmark advancements have been made using precious metal, earth-abundant metal, and biocatalysis across both heterogeneous and homogeneous systems, demonstrating the versatility of this chemistry. Despite a considerable increase in the number of publications in the area over the past decade, there remain several challenges and opportunities, and there is no doubt that advances will continue to be made. In accordance with the increasing global demand to preserve the finite resources on Earth, many earlier existing precious metal-catalyzed transformations have now been translated to the use of earth-abundant metal catalysts—a collective aim for researchers in the area. Thus, more elaborate and novel developments are to be expected in the coming years in this area. There remains an absence of biocatalysis for borrowing hydrogen C-alkylation processes, and asymmetric processes are poorly represented with respect to earth-abundant metal catalysis. Further collective targets that will continue to be sought are milder reaction conditions and lower catalyst

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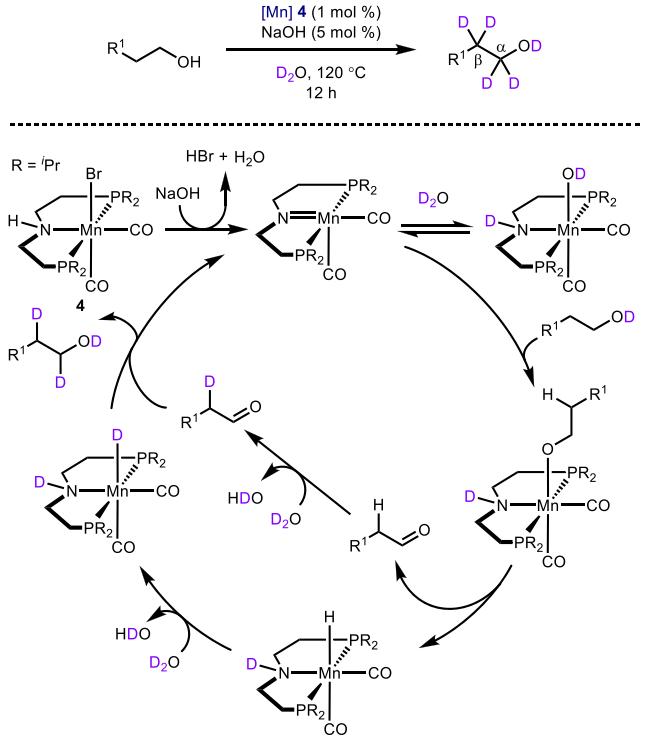
Scheme 20. Deuteration of Alcohols



loadings. We also anticipate more efforts targeting the design of new, more active catalysts for various processes as well as further implementation of the borrowing hydrogen methodology in dual-catalysis systems. Can alternative transformations and cascades be incorporated into borrowing hydrogen processes to create powerful novel one-pot transformations?[188] It is inevitable that many new and exciting borrowing hydrogen transformations will be discovered via these various avenues in the coming years. To close this outlook, we hope this article has conveyed the importance and usefulness of borrowing hydrogen for organic synthesis, and we envision a bright future for the area.

There remains an absence of biocatalysis for borrowing hydrogen C-alkylation processes, and asymmetric processes are poorly represented with respect to earth-abundant metal catalysis.

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#B.G.R.-B. and D.E.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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