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Enantioselective Borrowing Hydrogen: A Modern Tool to Construct Enantioenriched Molecules

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Abstract.

In the quest for the more rapid and eco-compatible preparation of complex molecules from widely available ones, borrowing hydrogen is one of the most elegant manners to directly functionalize alcohols. Such catalytic cycles reduce the synthetic cost, and avoid waste and additional steps associated with adjusting the redox state for the functionalization of carbon chains. In this field, the last ten years have seen the development of general strategies to control the absolute stereochemistry of the created molecules.

This enantiocontrol can arise from the three distinct steps of the catalytic cycle, namely the initial dehydrogenation, carbonyl functionalization or final hydrogen back-transfer. This review presents the different enantioselective approaches developed according to these principles and highlights the great potential of these transformations, the current limitations and future challenges.

Keywords: Enantioselective synthesis; Catalysis; Borrowing hydrogen; Hydrogen transfer; Redox economies

1 Introduction

Modern organic synthesis must accomplish multiple tasks: rapidly creating complex molecules of interest while minimizing the environmental impact and economic issues associated with the synthetic processes. This challenge becomes even more difficult when precise control over the stereochemistry of the resulting molecules is necessary. Borrowing Hydrogen (BH) is an approach of choice in order to rapidly generate complex molecules while limiting waste.¹ Typically, a borrowing hydrogen is a catalytic cycle involving an initial dehydrogenation of a saturated compound (alcohol) forming a transient unsaturated compound (carbonyl) (Figure 1.a). This dehydrogenation is most of the time catalyzed by a metal complex, leading to a metal dihydrogen catalytic intermediate. This one can either be a metal monohydride, di-hydride, or even a metal-dihydrogen complex (especially in the case of complexes with non-innocent ligands). In the context of this review, the intermediates are expressed as [Met]H₂ for clarity. The resulting unsaturated compound is now reactive, providing a new unsaturated species upon combination with another component (Figure 1.b). Importantly, the reactive unsaturated species is only formed in small amounts, corresponding at the maximum to the quantity of catalyst, which has a strong implication over the kinetics of its reaction with another partner. The consecutive hydrogen back-transfer from the metal/hydrogen complex finally generates the desired saturated product (Figure 1.c).

The first example of borrowing hydrogen can be traced back to the end of the 19th century with the discovery of the auto-condensation of alcohols by Guerbet.² Since then, this approach has been applied in numerous organic processes, constructing a wide array of molecular scaffolds of interest. It is notably largely applied by using simple alcohols as alkylating reagents, especially for amines or ketones. However, it was only recently that researchers started looking at borrowing hydrogen as a potential approach to enantioselectively create chiral molecules.³

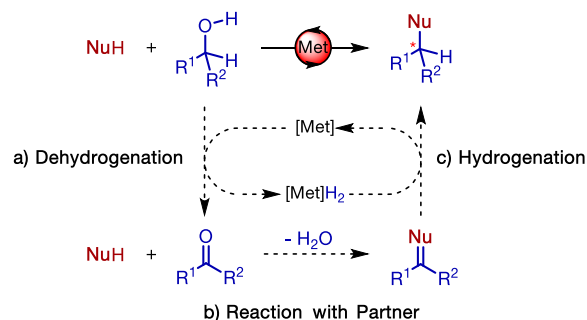


Figure 1. Typical Borrowing Hydrogen (BH).

While the power of BH for synthesis has long been demonstrated, before 2013, it was not explored in the context of controlling the absolute configuration of the products aside from an isolated pioneering example by Williams.⁴ The years 2013-2014 saw the generalization of the concept of enantioselective BH, notably by a report from our group on the efficient enantioselective functionalization of allylic alcohols through multicatalysis, and by Zhao on a general enantioselective alcohol amination.^{5,6} These studies

demonstrated the potential of BH for controlling chirality as a general approach, which subsequently led to the discovery of numerous useful other transformations over the last years.

As mentioned above, borrowing hydrogen transformations are based on a common catalytic cycle involving three steps. Consequently, it is possible to control the chirality of the newly formed molecule at each step (Figure 2), through:

- 1) An enantiodetermining dehydrogenation, for example by the desymmetrization of a *meso*-diol (Figure 2.a).
- 2) Enantiocontrolled addition of a nucleophile on the transient carbonyl, for example on an α,β -unsaturated aldehyde, notably using a second catalyst (Figure 2.b).
- 3) Enantioselective back hydrogen transfer on the resulting functionalized unsaturated compound, for example on a pro-chiral imine (Figure 2.c).

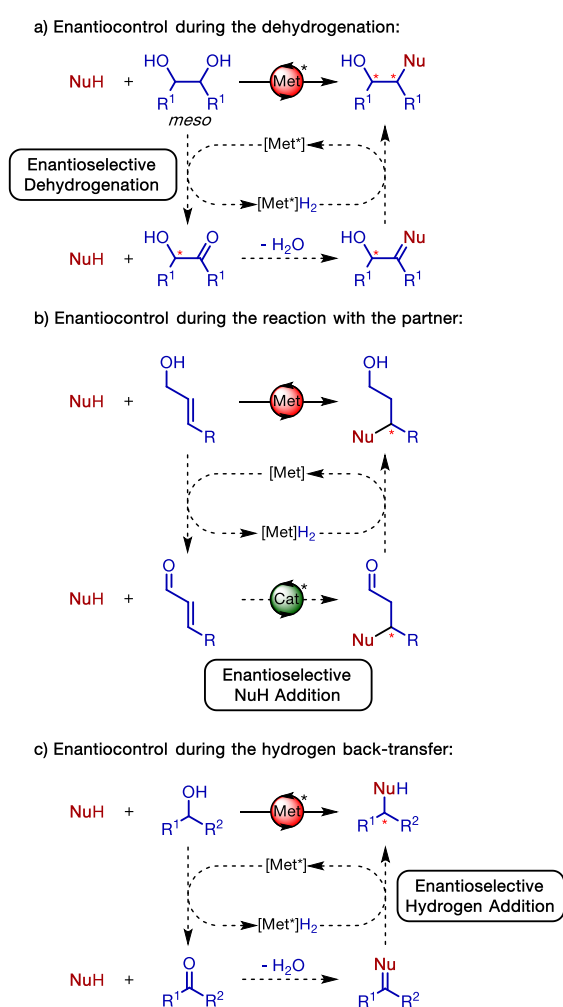


Figure 2. Possible strategies for successful enantiocontrol over a borrowing hydrogen reaction.

While the two latter steps have now been widely exploited for the enantiocontrol during the BH, the dehydrogenation approach remains under-exploited. Lately, several groups have demonstrated that several stereoselective events could be combined, providing the tools necessary to control independently multiple

stereogenic centers, notably through the application of the principles of multicatalysis.

Given the complexity of the borrowing hydrogen catalytic cycles, controlling the enantioselectivity faces numerous challenges. Many BH, especially the alkylation of amines using alcohols, are performed at relatively high temperatures, further increasing the difficulty in controlling the enantioselective event with the chiral catalyst. If the different steps of the catalytic cycles are in equilibrium, there is a possibility of product racemization. Finally, when developing a multicatalytic BH, catalyst compatibility must be taken into account, ensuring that all catalysts are working efficiently together without any mutual inhibition.

Anestis Alexandridis was born in Athens, Greece, and studied Organic Synthesis at the Université Grenoble-Alpes. He obtained his PhD in 2024, working under the supervision of Dr. Adrien Quintard at Aix-Marseille Université and then at Université Grenoble-Alpes.



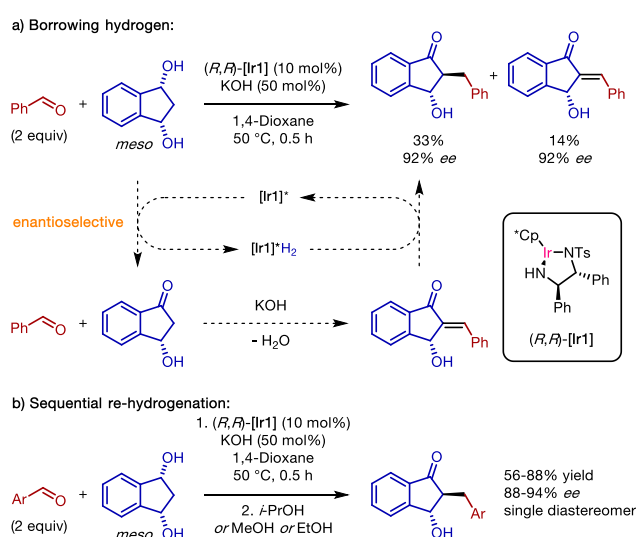
Adrien Quintard, CNRS researcher at the Université Grenoble-Alpes, did his studies at Castres and Lyon before obtaining in 2011 his PhD at the University of Geneva. After a postdoctoral stay at Stanford, he came back to France at Aix-Marseille Université where he obtained an associate researcher and then a CNRS position. In 2022, he moved to the Université Grenoble-Alpes where he continues developing new catalytic transformations and applying catalysis to complex systems such as molecular machines.



This review presents the different approaches that have been developed over nearly one decade by applying these principles for successful enantioselective reactions. Through such strategies, multiple key organic fragments have been efficiently prepared, notably featuring ketone, alcohol or amine functions. This review focuses on homogeneous catalysis, notably using metal complexes for the reversible (de)hydrogenation; therefore, reactions using enzymes will not be covered herein.⁷ We hope that this comprehensive review will help the reader apply the approach of enantioselective BH in synthesis. In addition, we also highlight important features concerning the current limitations of some of the approaches, hoping that this will help in the future development of improved or original enantioselective BH transformations.

2 Enantioselective Borrowing Hydrogen through Enantiocontrolled Dehydrogenation

While enantiocontrolled dehydrogenation has been scarcely applied in borrowing hydrogen, quite surprisingly, one of the earlier examples of enantioselective BH was reported by the group of Suzuki by relying on such an approach (Scheme 1).⁸ Indeed, in 2013, this group discovered that a prochiral *meso*-1,3-diol could be enantioselectively condensed with aldehydes. The key step in this catalytic cycle is the dehydrogenation by a simple chiral iridium complex (*R,R*)-[Ir1]. This enantioselective step of the catalytic cycle generates a reactive substrate encompassing a mono-ketone and a stereogenic secondary alcohol. In the presence of a base (KOH), this ketone reacts with the aldehyde to generate an enone, finally back-hydrogenated to the final alkylated compound, obtained in 92% *ee*. Isolation of a small amount of enone (also in 92% *ee*) confirmed that the enantiocontrol was arising from the initial dehydrogenation, while the hydrogen back-transfer on the enone is diastereoselective (99:1 *dr*). It was subsequently found more synthetically useful to add a hydrogen donor such as isopropanol, methanol, or ethanol upon the completion of the borrowing hydrogen in order to hydrogenate this small amount of enone formed to the desired product and obtain better yields.



Scheme 1. Desymmetrization and functionalization of *meso*-diols.

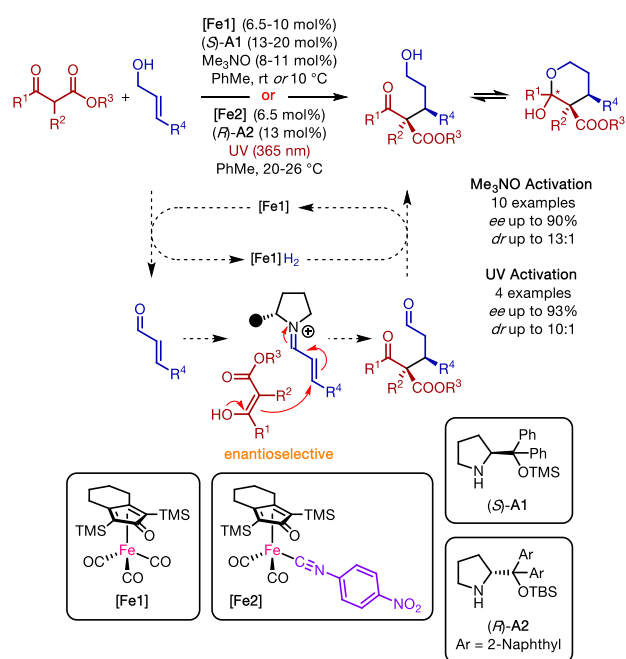
While of great potential interest, such an approach based on an enantiodiscriminating dehydrogenation event has not been further applied in BH.

3 Enantioselective Borrowing Hydrogen through Enantiocontrol During the Reaction with the Partner

3.1 Metal-Organocatalysis

The second step in a borrowing hydrogen is the reaction of the generated unsaturated species with another electrophilic or nucleophilic partner or function. In this context, our group discovered that such an event could be the source of enantiocontrol in a borrowing hydrogen transformation. However, since this individual event is not induced by the metal complex responsible for the reversible dehydrogenation, a strategy taking advantage of another chiral catalyst had to be implemented.

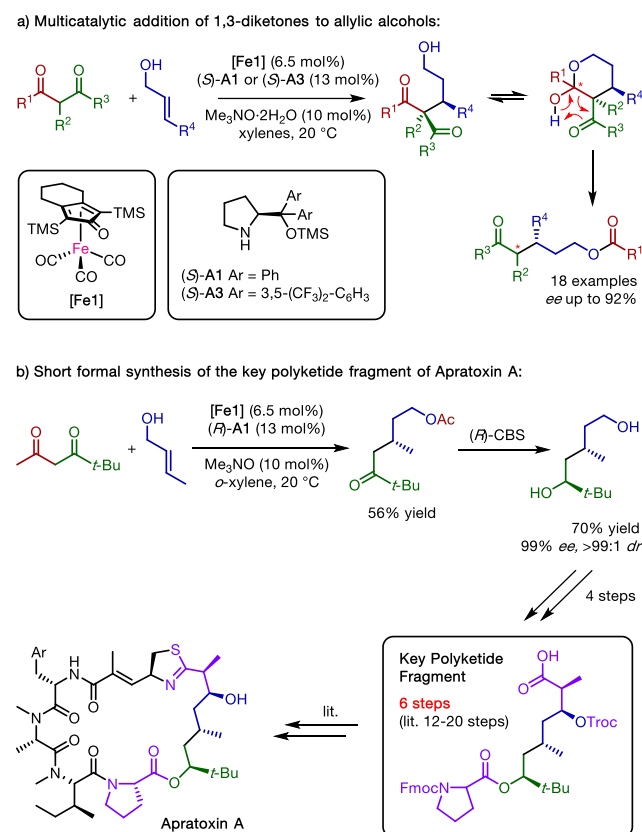
Such a multicyclic strategy was developed in 2013 for the enantioselective functionalization of allylic alcohols, one of the first efficient and general enantioselective BH (Scheme 2).⁹ This reaction implied the application of a chiral secondary amine organocatalyst (*S*)-A1. From the small amount of α,β -unsaturated aldehyde generated upon allylic alcohol dehydrogenation by the metal complex, the chiral organocatalyst induces an enantioselective 1,4-addition of a keto-ester, generating an enantioenriched aldehyde which is in turn back-hydrogenated to the final product by the metal hydride. Using keto-esters as nucleophiles, the obtained products, in equilibrium between ketone and lactol forms, are obtained with up to 90% *ee*. Aside from demonstrating the potential of multicyclic catalysis for borrowing hydrogen, interestingly, this study was the first to apply a cheap iron catalyst (here an iron cyclopentadienone complex) for a borrowing hydrogen, which also paved the way for the development of cheaper BH transformations based on less expensive metals.¹⁰ It is of great importance that the use of this iron complex allows to perform the borrowing hydrogen under mild conditions (10-25°C), a key parameter for optimal enantiocontrol during the organocatalyzed addition.



Scheme 2. Multicatalytic enantioselective functionalization of allylic alcohols by BH.

More recently, it was found that modifying the iron complex **[Fe1]** by replacing one CO ligand by an isonitrile, an efficient photo-induced borrowing hydrogen could be performed using **[Fe2]** (Scheme 2).¹¹ This circumvents the use of a small amount of Me₃NO for the initial CO abstraction to generate the active iron dehydrogenation catalyst.

From the initial reaction, the multicatalytic borrowing hydrogen functionalization of allylic alcohols was extended to the use of diketones as nucleophiles (Scheme 3.a).¹² Interestingly, the obtained adducts spontaneously rearranged through a retro-Claisen fragmentation, leading to products containing on one side a mono-ketone and on the other one a protected alcohol. Once again, the enantiocontrol of the overall BH is governed by the secondary amine organocatalyst during the Michael addition. The synthetic interest of this reaction and the synthetic economies it enables were demonstrated recently in the synthesis of the key polyketide fragment of the anticancer natural product apratoxin A (Scheme 3.b).¹³ Through this BH functionalization of an allylic alcohol, the preparation of this key fragment was accomplished in only 6 steps while the five prior literature reports required 12 to 20 steps.

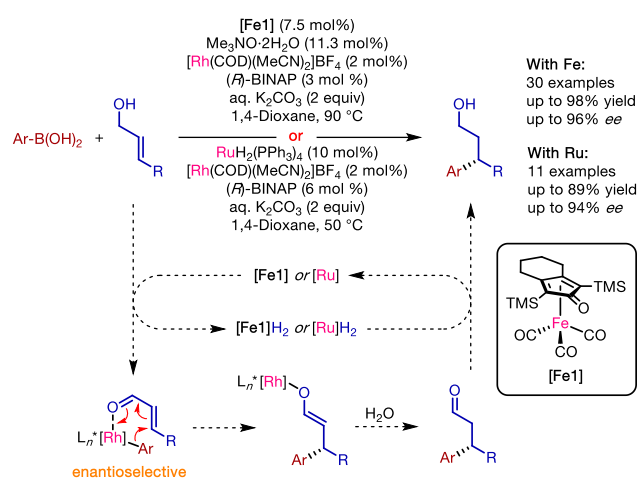


Scheme 3. Addition of diketones to allylic alcohols through multicatalytic BH and short synthesis of the key Apratoxin A polyketide fragment.

In order to accelerate the Michael addition and improve the enantiocontrol, it was later found that adding a copper salt as a third catalyst improved both the yield and enantioselectivity in this transformation.¹⁴ In addition, this triple catalytic approach also allowed to expand the scope in terms of nucleophiles, notably to nitro- and sulfo-esters.

3.2 Metal-Metal Catalysis

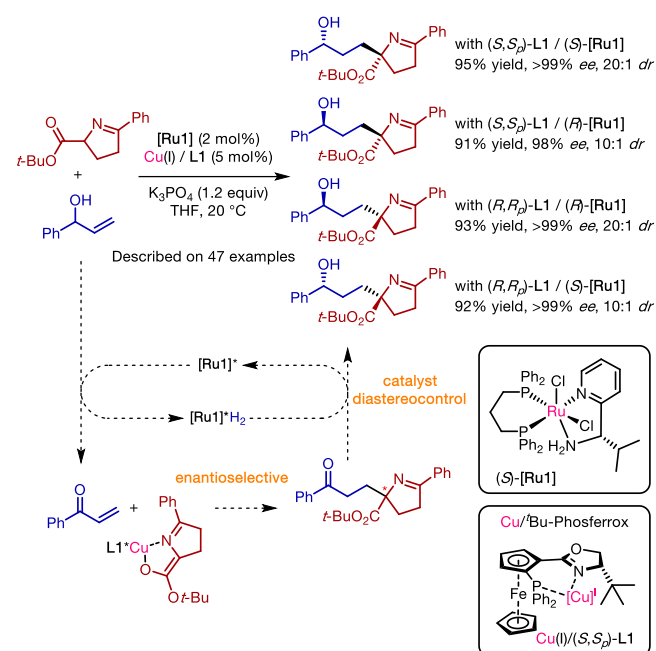
Taking advantage of this principle of multicatalytic functionalization of allylic alcohols, the group of Dydio extended this reactivity to the addition of aryl boronic acids (Scheme 4).¹⁵ Similarly to the above example, an achiral metal complex (iron- or ruthenium-based) is responsible for the dehydrogenation of the allylic alcohol to an α,β -unsaturated aldehyde. This aldehyde subsequently undergoes a chiral rhodium complex-catalyzed 1,4-addition of the aryl nucleophile providing the enantioenriched aldehyde, which is in turn back-hydrogenated by the metal hydride. Through such a metal-metal combination, a broad range of useful primary alcohols could be generated with up to 96% *ee*.



Scheme 4. Addition of aryl boronic acids to allylic alcohols through multicatalytic BH.

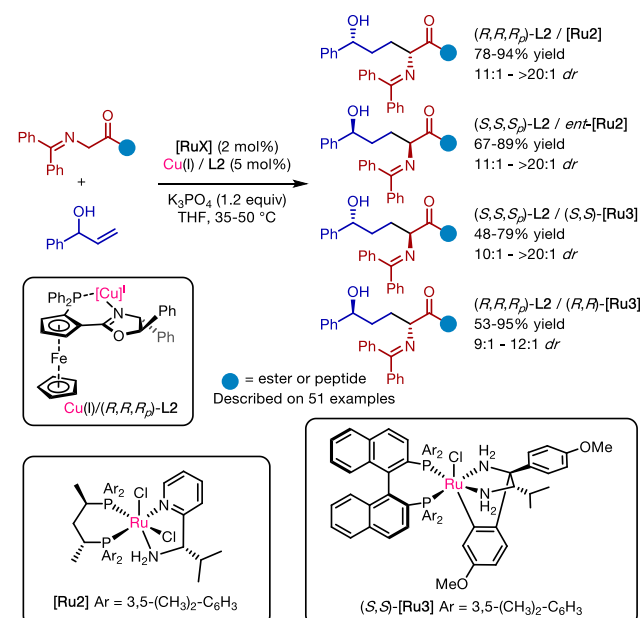
In 2022, the team of Wang further complexified the multicatalytic system by combining two chiral metal complexes (Scheme 5).¹⁶ The aim of such a combination was to independently control two different stereogenic centers in the addition of ketimine esters to secondary allylic alcohols. Once again, ruthenium complex (*S*)-[Ru1] induces the formation of the reactive enone from a racemic secondary allylic alcohol. The enone then undergoes 1,4-addition of the ketimine ester. Using a chiral copper complex controls the tetra-substituted stereogenic center generated in this enantioselective event. From the Michael adduct, a second diastereocontrolled event occurs, namely the back-hydrogenation of the ketone, thus generating the stereogenic secondary alcohol. These two events are independently controlled by the two chiral catalysts, so that all possible stereoisomers of the products can be prepared with equal efficiency. As a result, such a reaction demonstrates all the power of multicatalysis

and the potential of combining multiple stereocontrolling events in a borrowing hydrogen.



Scheme 5. Stereodivergent addition of ketimine ester nucleophiles to allylic alcohols through multicatalytic BH.

Recently, the same group extended this strategy to the addition of non-substituted ketimine esters (Scheme 6).¹⁷ This reaction is notably interesting since it enables the addition of pro-nucleophiles containing peptidic chains, which is of great synthetic interest.



Scheme 6. Stereodivergent addition of ketimine ester nucleophiles to allylic alcohols through multicatalytic BH.

Similarly to the previous examples, while the enantioselectivity of the reaction is controlled through

the copper-catalyzed 1,4-addition, the ruthenium complex independently controls the hydrogen back-transfer, enabling the convenient access to all possible stereoisomers of the product.

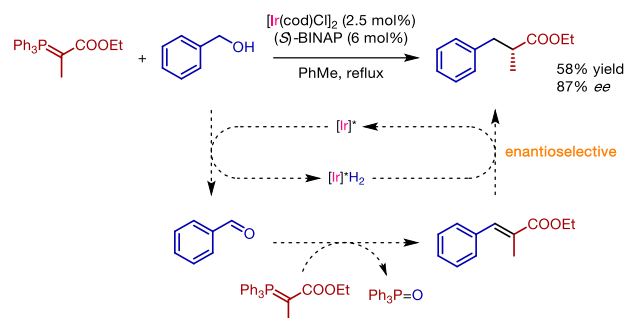
4 Enantioselective Borrowing Hydrogen through Enantiocontrolled Hydrogen Back-Transfer

The last step of a borrowing hydrogen catalytic cycle implies the hydrogen back-transfer from the generated metal/hydrogen complex to the functionalized unsaturated compound. Given the long history of enantioselective hydrogenation and the wide array of available efficient catalysts for alkene, ketone and imine hydrogenation, it is not surprising that most enantioselective borrowing hydrogen transformations have relied on an enantiocontrolled hydrogen back-transfer by a chiral metal catalyst. As a result, numerous enantioselective BH were developed following this principle, enabling notably C–C bond formation or the classical *N*-alkylation, using alcohols as pro-electrophiles. Through the appropriate implementation of chiral metal complexes, exquisite levels of enantiocontrol could be achieved in these transformations easily providing synthetically useful molecules.

4.1 C–C Bond Formation using Alcohols as Pro-Electrophiles

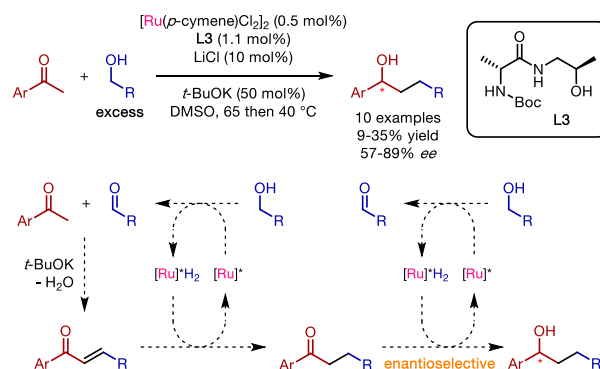
4.1.1. Carbonyls as Pro-Nucleophiles in Alkylation using Alcohols

The pioneering example of enantioselective BH through enantiocontrolled hydrogen back-transfer was disclosed by the group of Williams in 2007.⁴ In this transformation reported on one single example, benzyl alcohol is dehydrogenated by the iridium complex, generating benzaldehyde, which engages in a Wittig reaction to form an intermediate alkene. From here, by using the simple combination of [Ir(COD)Cl]₂ and (*S*)-BINAP, the hydrogen back-transfer to the substituted alkene provided the desired enantioenriched product in 58% yield and 87% *ee*. While not optimal, this study was the first demonstration of the potential of borrowing hydrogen for the direct generation of enantioenriched scaffolds.



Scheme 7. Enantioselective Wittig-type alkylation using alcohols.

From this first example, it was only in 2014 that other groups started focusing on the application of this principle to other transformations. First, Adolffson and colleagues developed the condensation of ketones with alcohols (Scheme 8).¹⁸ In this process, the final enantioselective hydrogenation of the ketone resulting from the BH provided the secondary alcohol-containing products in 57–89% *ee*. It must be pointed out that in this case, the BH is not truly enantioselective in itself. Indeed, the direct product of the BH is the achiral ketone obtained upon alkylation with the aldehyde generated from the alcohol and the subsequent alkene back hydrogenation. However, since a large excess of alcohol is used, an enantioselective transfer hydrogenation occurs between the excess alcohol and the ketone.

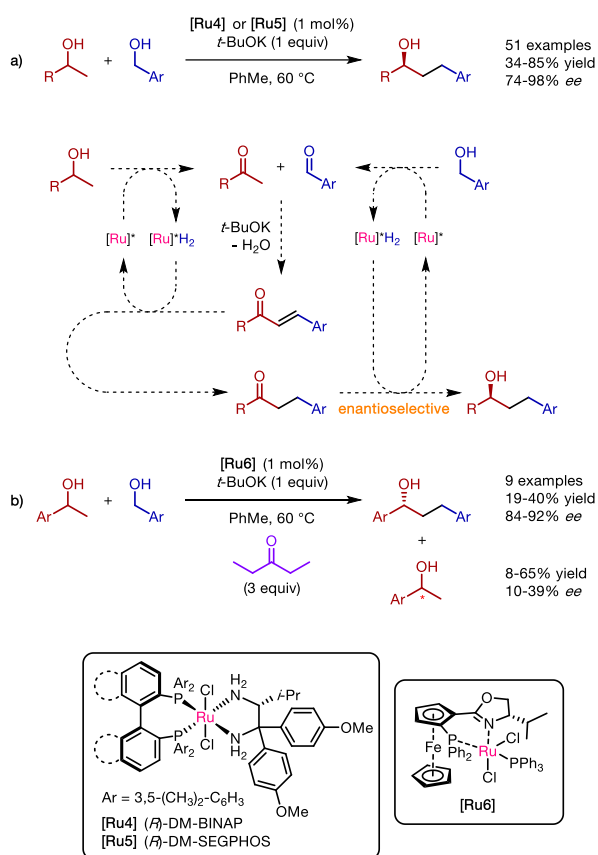


Scheme 8. Alkylation of ketones with alcohols and subsequent ketone hydrogenation.

One of the solutions to obtain a true enantioselective BH through intermediate ketone alkylation, was to start from a mixture of a secondary and a primary alcohol. In 2020, the groups of Wang and Zhao concomitantly reported this kind of reactivity (Scheme 9).

Wang and co-workers could perform such a combination using chiral ruthenium catalysts [**Ru4-5**] ligated with both a chiral diphosphine and a chiral diamine ligand (Scheme 9.a).¹⁹ The resulting elongated secondary alcohols were generated in 74–98% *ee*. On the other side, the team of Zhao

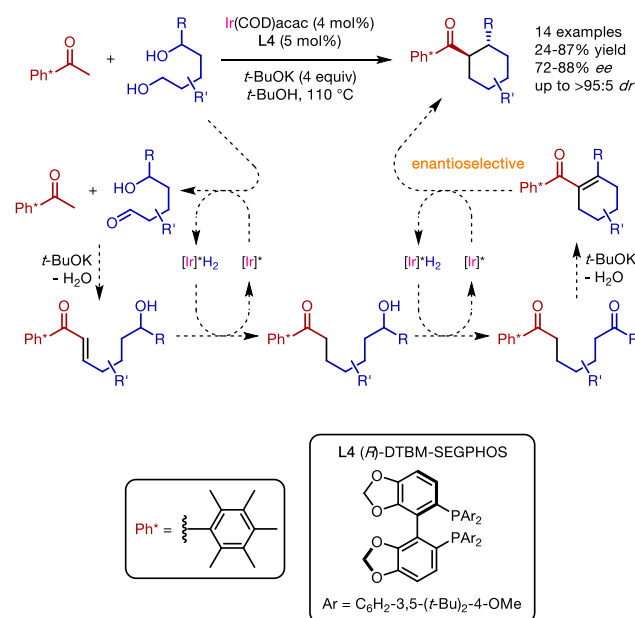
subsequently used ruthenium catalyst **[Ru6]** featuring a chiral phosphine-oxazolidinone ligand to obtain the final alcohols in 84-92% *ee* (Scheme 9.b).²⁰ In Zhao's work, 3-pentanone is added to the reaction to facilitate reversible hydrogen transfers. It is important to mention that in both cases, the obtained elongated secondary alcohols are enantiomerically stable over time under the reaction conditions, probably because of the increased steric hindrance around the produced alcohol when compared to the starting one. Interestingly, Zhao also observed that a kinetic resolution of the reacting secondary alcohols was occurring, with one enantiomer of the starting material being partially recovered in 10-39% *ee*.



Scheme 9. β -Alkylation of secondary alcohols with primary alcohols.

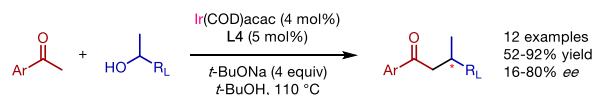
In 2019, the group of Donohoe reported another cascade to induce enantioselective alkylation through BH. The strategy consisted in alkylating twice a ketone using racemic diols (Scheme 10).²¹ Key to success was the implementation of a simple chiral diposphine-ligated iridium complex, as well as the use of the sterically demanding pentamethylphenyl ketone. The reaction pathway involves two successive borrowing hydrogen catalytic cycles. In the first one, the ketone condenses with the primary alcohol through aldehyde formation, then aldol reaction/dehydration occurs, followed by hydrogen back-transfer to the alkene. From this first intermediate, a similar second sequence

from the secondary alcohol induces the formation of the final chiral ketones in 72-88% *ee* upon final back-hydrogenation of the tetrasubstituted alkene. This alkene hydrogenation is a two-step process involving 1,4-hydride addition followed by protonation, explaining the formation of the major *anti*-adduct.



Scheme 10. Enantioselective alkylation of pentamethylphenyl ketone with diols.

Finally, in 2020, Donohoe and co-workers extended this concept to the intermolecular condensation of bulky aromatic ketones with racemic secondary alcohols (Scheme 11).²² Using the same chiral iridium complex, the alkylated ketones were obtained in up to 80% *ee*. One of the major limitations of this transformation is the necessity of secondary alcohols featuring on one side a methyl group and on the other one a bulky alkyl chain such as a *tert*-butyl substituent in order to obtain good enantioselectivity. Aside from this limitation, it is of great synthetic interest that the bulky aromatic substituent of the ketone can be easily cleaved, notably to provide the corresponding primary alcohol, ester or amide.

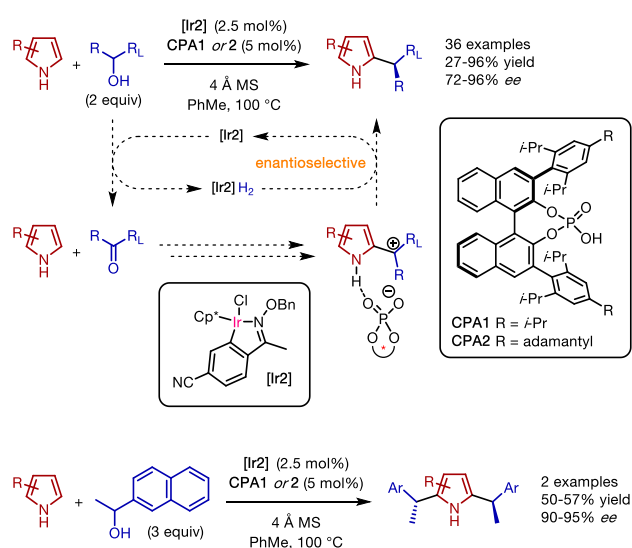


Scheme 11. Enantioselective alkylation of aromatic ketones using secondary alcohols.

4.1.2. Heterocycles as Nucleophiles

In order to create a C–C bond employing alcohols as pro-electrophiles by exploiting their electrophilicity at the carbonyl level, nucleophiles other than ketones can be used.

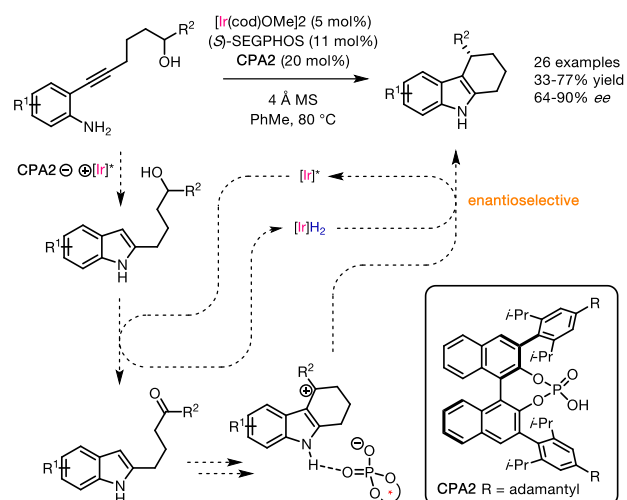
In 2021, the team of Zhao found that pyrroles could be condensed with secondary alcohols to generate mono- or di-alkylated chiral pyrroles (Scheme 12).²³ In a classical borrowing hydrogen mechanism, this catalytic cycle involves a metal-catalyzed dehydrogenation of the alcohol to the ketone, pyrrole addition, dehydration and hydrogen back-transfer to the newly formed unsaturated compound. Using achiral iridium complex **[Ir2]** and chiral phosphoric acid organocatalysts (**CPA1-2**, *vide infra*), this hydrogen back-transfer occurs with good to excellent enantiocontrol (72–96% *ee*). In the enantiodiscriminating step, the phosphoric acid is believed to protonate the pyrrole, creating the appropriate chiral environment for subsequent re-hydrogenation by the metal catalyst. This reaction is of great synthetic importance since the substituted pyrrole scaffolds can be found in numerous bioactive compounds.



Scheme 12. Alkylation of pyrroles using secondary alcohols.

Concomitantly, the same team disclosed an intramolecular cascade from molecules featuring a primary amine, an alkyne and a racemic secondary alcohol (Scheme 12).²⁴ At the onset, the chiral Lewis acidic iridium complex activated by a chiral phosphoric acid, triggers the cyclization of the amine on the alkyne. From the resulting indole, a borrowing hydrogen catalytic cycle involves generation of the carbonyl, intramolecular addition of the indole, dehydration, followed by the final enantioselective hydrogen back-transfer. The combination of the chiral

phosphoric acid and the SEGPHOS-ligated chiral iridium complex is crucial to obtain the desired reactivity and enantioselectivity. As a result, a wide array of substituted free indoles could be efficiently and easily constructed in up to 90% *ee*.



Scheme 13. Tandem intramolecular cyclization/alkylation by borrowing hydrogen and chiral phosphoric acid catalysis.

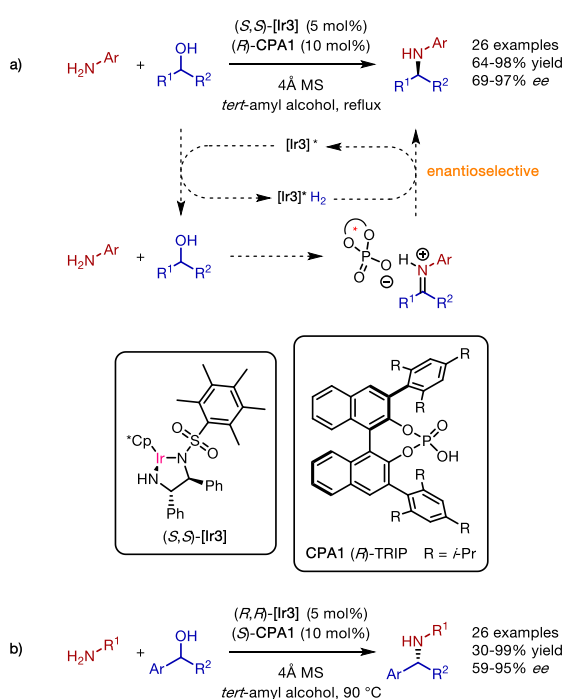
4.2. N-Alkylation using Alcohols as Pro-Electrophiles

One of the most common borrowing hydrogen reactions is the use of alcohols to alkylate amines, liberating water as sole by-product. This transformation follows the classical catalytic cycle of alcohol dehydrogenation, condensation of the carbonyl with the amine, and hydrogen back-transfer. If secondary alcohols are used, the hydrogenation of the transient imine provides chiral amines. As a result, it is not surprising that numerous groups have taken advantage of an enantioselective hydrogen back-transfer to control the chirality on these amines.

4.2.1 N-Alkylation using mono-Alcohols as Pro-Electrophiles

In the field of *N*-alkylation, the major breakthrough came in 2014 when the group of Zhao developed the first general enantioselective amination using racemic secondary alcohols (Scheme 14.a).⁶ Key to success was the discovery of a multicatalytic combination of chiral iridium complex (*S,S*)-**[Ir3]** and chiral phosphoric acid **CPA1**. The synergistic combination of these two catalysts ensures a maximal enantiodiscrimination during the hydrogen back-transfer to the imine which is protonated by the chiral phosphoric acid. Through such a mechanism, the desired chiral amines are prepared starting from

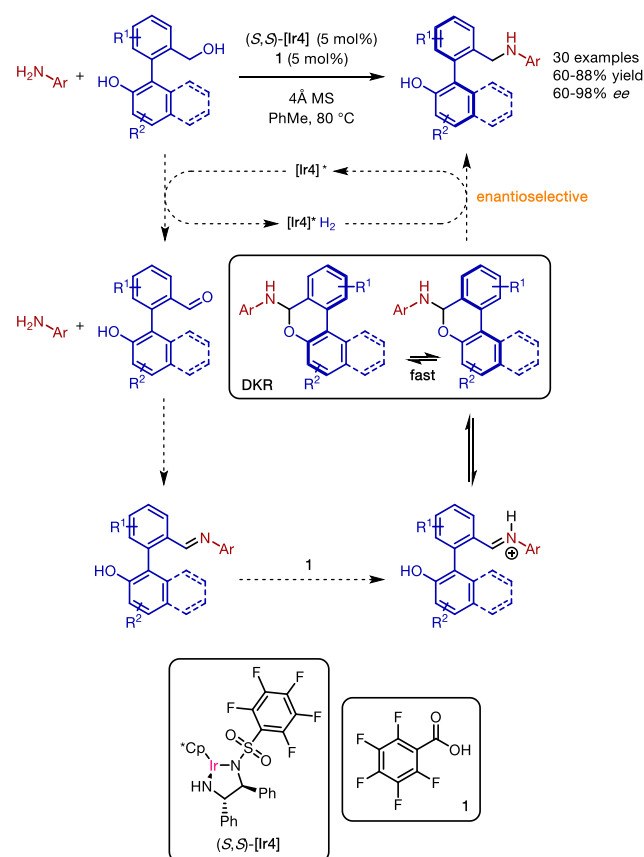
anilines in 69-97% *ee*. Importantly, these excellent levels of enantiocontrol can be attained despite the reaction taking place at relatively high temperatures (100 °C). The demonstration of the power of such a multicyclic combination of a metal complex and a chiral phosphoric acid activating the transient imine, paved the way for the development of a multitude of enantioselective *N*-alkylations through borrowing hydrogen. Recently, the same team expanded the scope of similar multicyclic combinations to the use of aliphatic amines as nucleophiles (Scheme 14.b).²⁵



Scheme 14. First efficient enantioselective *N*-alkylation using multicyclic catalysis (a) and expansion to aliphatic amines as nucleophiles (b).

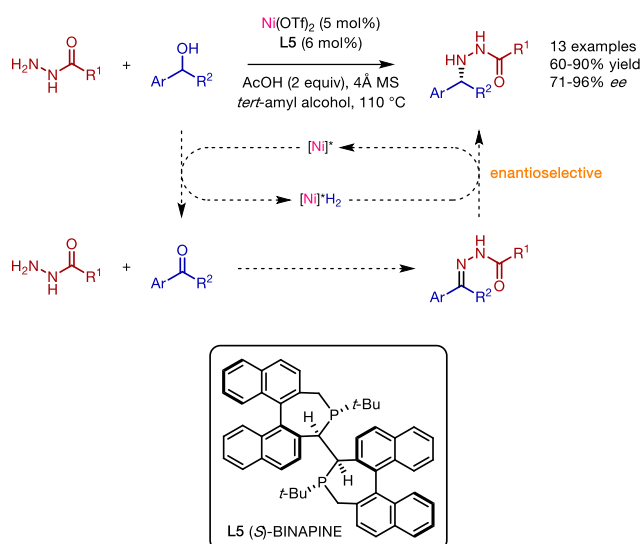
In 2018, the team of Wang took advantage of the use of a chiral iridium complex in combination with an achiral Brønsted acid catalyst **1** to access enantioenriched atropisomers through the enantioselective amination of biaryls (Scheme 15).²⁶ The racemic starting biaryls featured a primary benzylic alcohol on the upper part reacting in the BH and a phenol on the lower part. Upon primary alcohol dehydrogenation by the metal complex, the formed aldehyde could condense with the aromatic amine to generate an intermediate imine. Through reversible cyclization with the phenol, the two enantiomers of the imine could rapidly interconvert, while the final enantioselective hydrogen back-transfer occurred preferentially on one of the two enantiomers. Through this Dynamic Kinetic Resolution, the final amines were generated in up to 98% *ee*. As a result, this study demonstrated the potential of enantioselective BH to

construct other scaffolds, such as compounds possessing a key axial chirality.



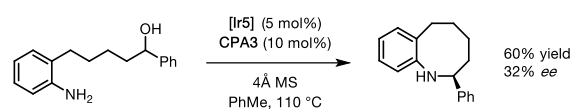
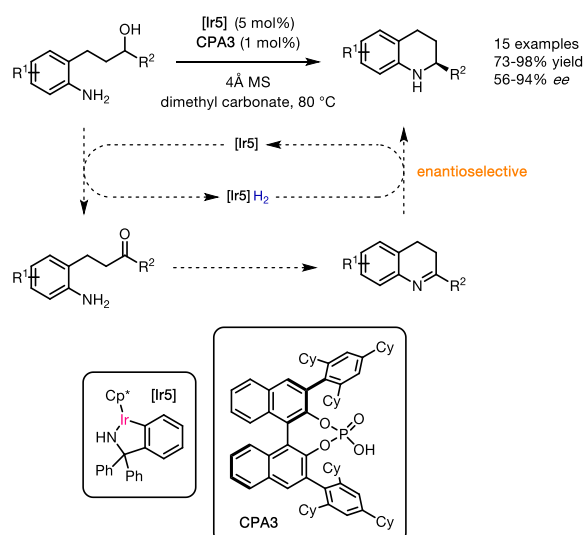
Scheme 15. Enantioselective *N*-alkylation of biaryls.

Aside from iridium complexes, in 2017, Tang, Zhou and co-workers were able to apply cheaper metal sources for an enantioselective *N*-alkylation (Scheme 16).²⁷ Using a complex generated from Ni(OTf)₂ and (*S*)-BINAPINE (**L5**), hydrazides could be efficiently condensed with racemic secondary alcohols. The use of this highly complex diphosphine ensured the generation of the alkylated hydrazides in optimal 71-96% *ee*. This study demonstrated the potential of employing less expensive metals for enantioselective *N*-alkylation using alcohols, which should inspire the development of other related transformations relying on more common metal sources.



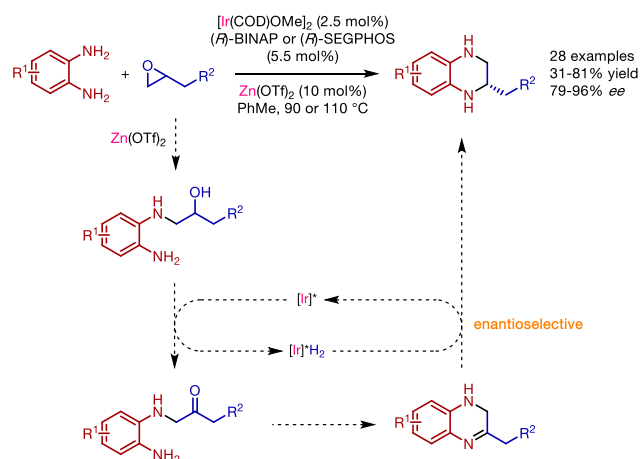
Scheme 16. Enantioselective *N*-alkylation of hydrazides employing a nickel-based chiral complex.

Aside from intermolecular versions, the intramolecular *N*-alkylation has also been studied. In 2014, Zhao and co-workers had reported a single example of such a transformation in 68% *ee*,⁶ and in 2017, they further optimized and generalized this transformation to access efficiently a variety of tetrahydroquinolines (Scheme 17).²⁸ The combination of an achiral iridium complex **[Ir5]** and a chiral phosphoric acid catalyst **CPA3** were key to success. The phosphoric acid generates the appropriate chiral environment around the protonated intermediate imine, favoring the preferential addition of hydrogen from the metal complex on one face. Consequently, the tetrahydroquinolines, useful scaffolds present in numerous natural products, were formed in up to 94% *ee*. It is noteworthy that the reaction could even be applied to generate an 8-membered-ring amine, albeit in a moderate 32% *ee*.



Scheme 17. Enantioselective intramolecular *N*-alkylation for the preparation of tetrahydroquinolines.

In order to develop a convenient and economical route to tetrahydroquinoxalines, the same group developed a cascade reaction between aromatic diamines and racemic epoxides (Scheme 18).²⁹ The reaction involves an initial $\text{Zn}(\text{OTf})_2$ -catalyzed epoxide opening at the less hindered position by one of the amines. From the generated secondary alcohol, a classical borrowing hydrogen featuring the enantioselective hydrogen back-transfer by the chiral iridium catalyst generates the desired heterocycles.



Scheme 18. In-situ epoxide opening and borrowing hydrogen for the preparation of tetrahydroquinoxalines.

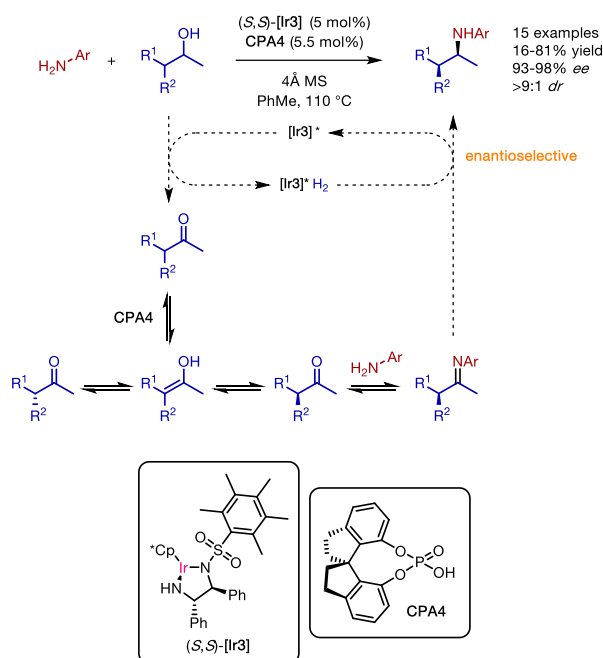
Through the synergistic action of the iridium complex and the Lewis acid co-activating the imine, this

enantioselective hydrogenation occurs with 79-96% *ee*, once again highlighting the importance of multicatalytic systems for the efficient *N*-alkylation of amines with alcohols.

4.2.2 *N*-Alkylation using Mono-Alcohols Featuring Two Contiguous Stereocenters

In the above-described classical borrowing hydrogen *N*-alkylation of amines using alcohols, a single stereogenic center is created based on the reactivity of a secondary alcohol. It was also found that stereocenters adjacent to the reactive secondary alcohols could also be controlled through BH.

Based on a combination of chiral iridium complex (*S,S*)-[Ir3] and chiral phosphoric acid co-catalyst CPA4, the team of Zhao reported in 2015 an enantioselective borrowing hydrogen controlling two adjacent stereocenters through a Dynamic Kinetic Resolution (Scheme 19).³⁰

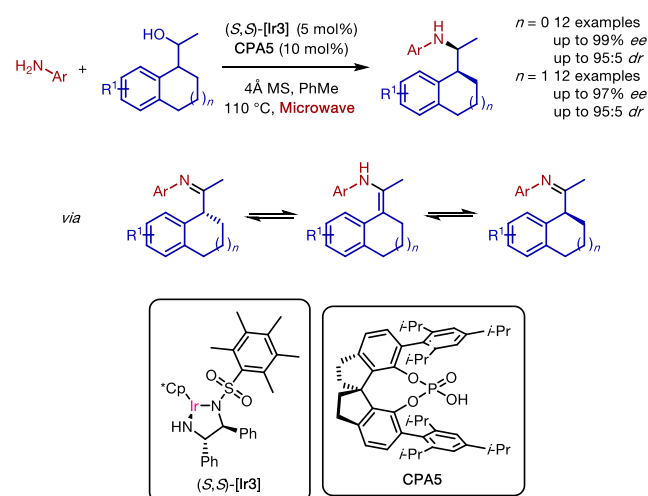


Scheme 19. Enantioselective DKR using alcohols for the *N*-alkylation of amines.

Starting from the racemic substrates possessing a secondary alcohol and an adjacent stereocenter (typically 2:1 *dr*), the dehydrogenation by the metal catalyst generates the reactive ketone. At this point, subsequent calculations seemed to indicate that the equilibrium between the different stereoisomers was occurring at the ketone level through enol formation and not through the corresponding enamine obtained upon condensation with the amine nucleophile as it was previously postulated.³¹ This racemization process is catalyzed by the chiral phosphoric acid. Once the imine is formed, one of the enantiomers reacts faster with the chiral iridium complex to

preferentially afford one final stereoisomer. In this hydrogen back-transfer, the chiral phosphoric acid also activates in a synergistic manner the imine through *N*-protonation to obtain optimal enantiocontrol. The exquisite levels of stereocontrol in such a complex process (>9:1 *dr* and >93% *ee*) further demonstrate the efficiency of this multicatalytic combination in borrowing hydrogen.

The power of this multicatalytic combination was further extended to secondary alcohols featuring adjacent tetraline or indane scaffolds (Scheme 20).³² The use of microwave irradiation was key to shortening the reaction time in such a process and obtaining appropriate diastereo- and enantio-control (up to >95:5 *dr* and >99% *ee*).

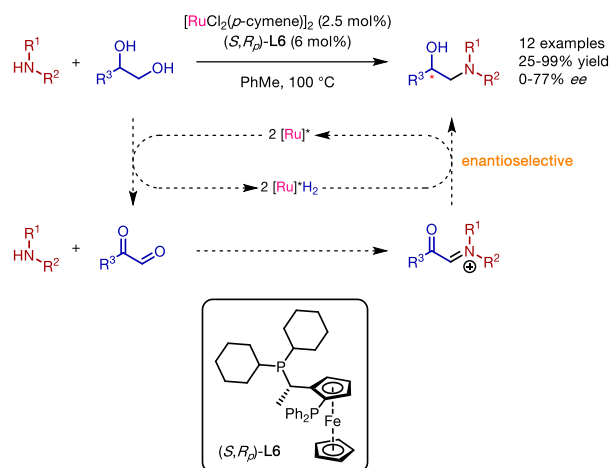


Scheme 20. Enantioselective DKR to access chiral tetralines.

4.2.3 *N*-Alkylation using Diols as Pro-Electrophiles

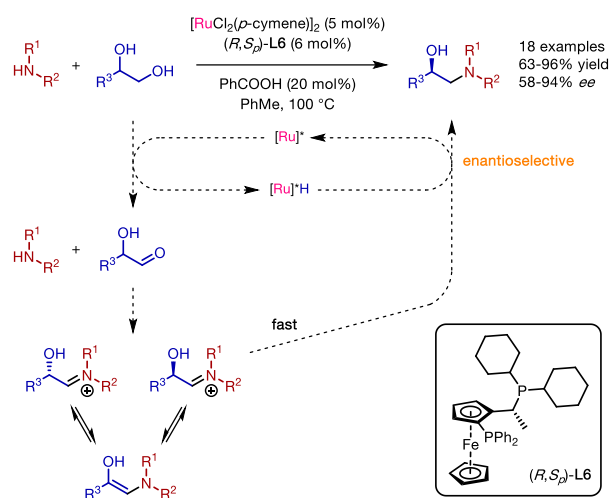
Aside from simple alcohols, the borrowing hydrogen-based *N*-alkylation was also largely studied starting from diols, providing access to an extensive range of useful nitrogen containing compounds, such as amino-alcohols, diamines or pyrrolidines.

In an early example, disclosed in 2013, the team of Oe, condensed cyclic secondary amines with racemic substrates featuring a primary alcohol and an adjacent secondary alcohol (Scheme 21).³³ It was believed that the postulated mechanism could have involved a double dehydrogenation of the diol to the corresponding oxo aldehyde, followed by subsequent enantioselective hydrogen back-transfer. The enantiocontrol was far from optimum using a simple combination of [RuCl₂(*p*-cymene)]₂ and a Josiphos ligand, providing the highly useful amino-alcohol products with moderate enantiocontrol (maximum 77% *ee*).



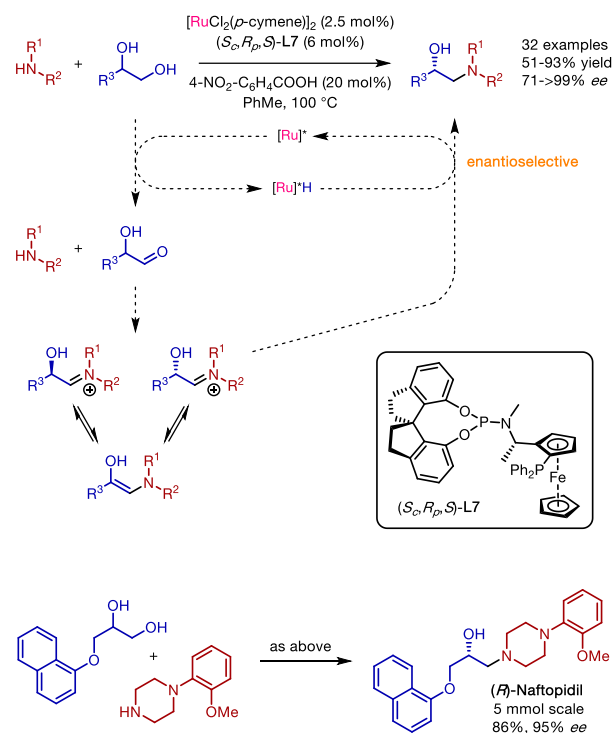
Scheme 21. Enantioselective condensation of cyclic secondary amines with diols.

With the knowledge on the possible activation of the intermediate imines by a Brønsted acid co-catalyst, the same reaction was studied again more recently by the group of Zhang and Zhao (Scheme 22).³⁴ Simply adding benzoic acid as co-catalyst to a mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ and a chiral diphosphine ligand considerably increased the enantioselectivity of the transformation. As a result, the borrowing hydrogen adducts were isolated in up to 94% *ee*. A preliminary mechanistic investigation concluded that the product was formed through a mechanism involving a dynamic kinetic asymmetric hydrogen back-transfer from the *in-situ* generated racemic aldehyde. Upon condensation of this aldehyde with the amine, an acid-catalyzed rapid racemization occurs through the achiral enamine, leading to the preferential formation of the desired enantiomer upon more rapid hydrogenation of one of the enantiomers of the imine.



Scheme 22. Enantioselective condensation of cyclic secondary amines with diols using benzoic acid as co-catalyst.

In 2021, the team of Ling and Zhong further optimized the same transformation by developing a novel ferrocenyl spiro-phosphoramidite ligand (S_C,R_p,S) -L7, specific for this transformation (Scheme 23).³⁵

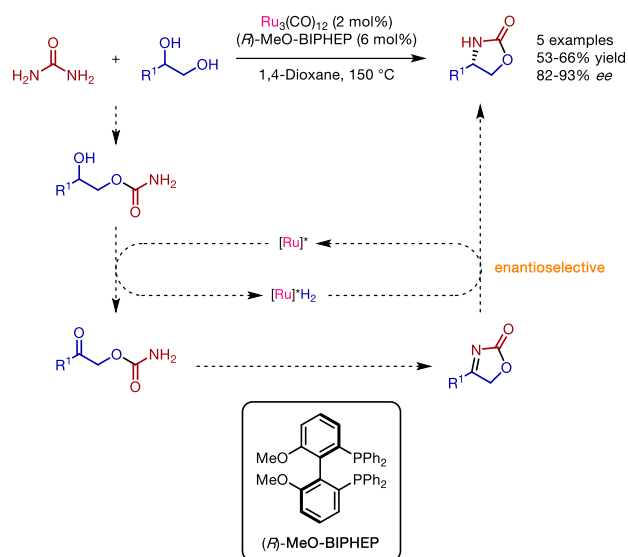


Scheme 23. Improved enantiocontrol using a novel ligand for the preparation of amino-alcohols.

Once again applying a Brønsted acid co-catalyst, the ruthenium complex generated upon coordination with this new ligand provided optimum enantiocontrol, furnishing a large scope of synthetically relevant amino-alcohols in up to >99% *ee*. Interestingly, the reaction conditions were also suitable for the enantioselective condensation of primary amines. Demonstrating its potential, this method was notably applied in the direct synthesis of bioactive (*R*)-Naftopidil.

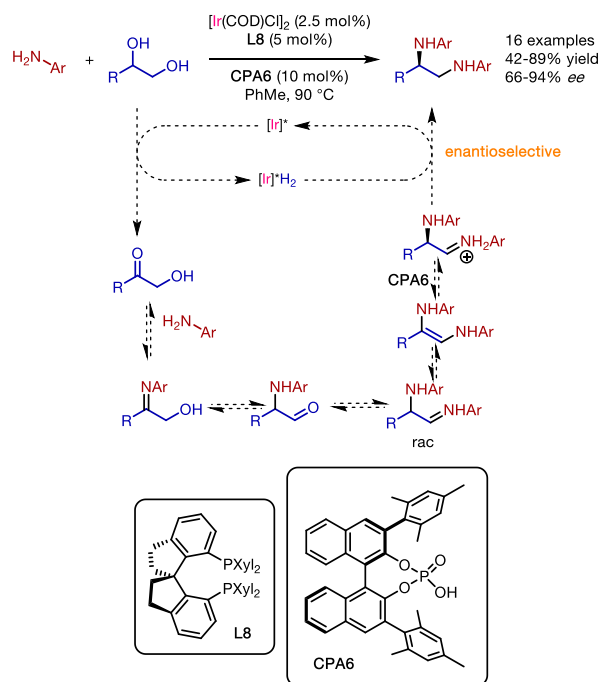
Aside from the preparation of amino-alcohols, other groups have exploited the reactivity of vicinal diols in enantioselective borrowing hydrogen transformations. In 2016, Beller and co-workers took advantage of the condensation of inexpensive urea with similar diols to prepare enantioenriched oxazolidin-2-ones (Scheme 24).³⁶ Such a reaction starts with the addition of the primary alcohol to urea, liberating ammonia while forming the key carbamate possessing an adjacent secondary alcohol. This alcohol subsequently enters the borrowing hydrogen cycle with intramolecular nitrogen addition on the intermediate aldehyde, followed by enantioselective hydrogenation. Use of a chiral diphosphine-ligated ruthenium complex afforded the resulting oxazolidin-2-ones in 82-93% *ee*, despite the high temperature (150 °C) required for the

transformation. It is worth mentioning that the reaction tolerated both aliphatic and benzylic alcohols with equal enantiocontrol.



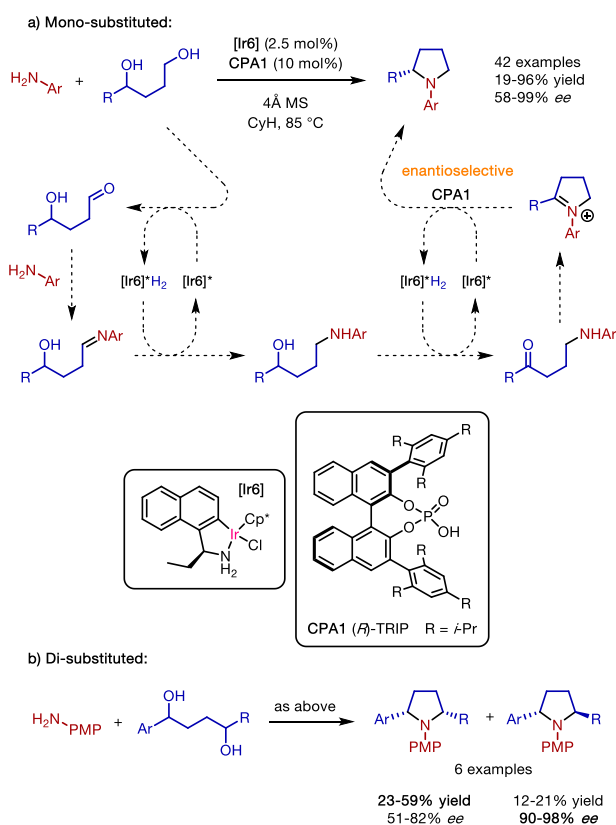
Scheme 24. Enantioselective synthesis of oxazolidin-2-ones from diols.

The reactivity of racemic diols with amines has also been advantageously used in order to prepare chiral diamines, another class of important organic scaffold. A transformation of this kind developed in 2021 is based on the double condensation of the primary amine with each of the alcohol functions (Scheme 25).³⁷ Applying a combination of an iridium complex chelated by chiral diphosphine ligand **L8** and chiral phosphoric acid **CPA6**, the diamines were generated in up to 94% *ee*. Control experiments revealed that the diamine was formed through a mechanism involving the dehydrogenation of only one of the alcohols and its condensation with the primary amine to form a first imine. In the presence of the Brønsted acid, this imine could equilibrate to the corresponding α -aminoketone, condensing again with another amine to form an amino-imine. Dynamic equilibrium between the two enantiomers of this amino-imine and preferential enantioselective hydrogenation of one of them could provide the final diamine with excellent enantiocontrol.



Scheme 25. Enantioselective synthesis of diamines from racemic diols.

Aside from vicinal diols, the condensation of primary amines to 1,4-diols was also developed in order to construct valuable pyrrolidines (Scheme 26).³⁸ These 1,4-diols react twice through the borrowing hydrogen to generate mono- or di-substituted pyrrolidines depending on the substitution of the starting diols. While present in many bioactive molecules, chiral ligands, or organocatalysts, these pyrrolidines are particularly difficult to synthesize, and this simple and direct method avoiding additional steps and waste constitutes an interesting advance towards their preparation. Once again, the enantiocontrol arises during the hydrogen back-transfer and is efficiently implemented through the combination of chiral iridium complex **[Ir6]** and chiral phosphoric acid **CPA1**. Consequently, a wide array of mono-substituted (Scheme 26.a), as well as more challenging di-substituted pyrrolidines (Scheme 26.b) can be obtained with exquisite enantiocontrol (up to 99% *ee*).



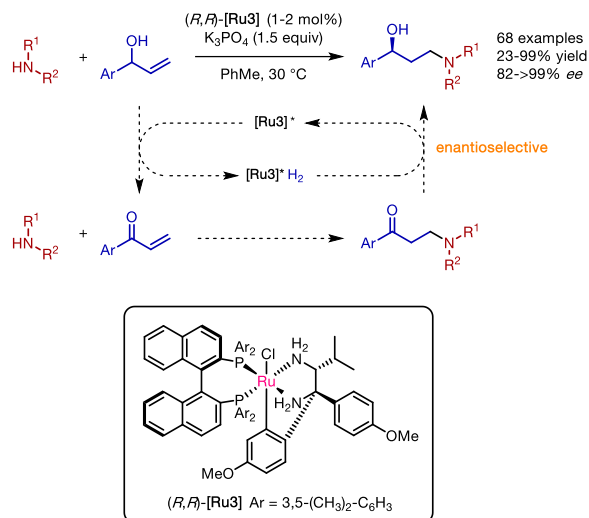
Scheme 26. Enantioselective synthesis of pyrrolidines from racemic 1,4-diols.

4.3. Conjugate Addition on Transient Michael Acceptors and Enantioselective Hydrogen Back-Transfer

The Michael addition disclosed in chapter 3 is not the only way to control enantioselectivity using allylic alcohols in borrowing hydrogen, and enantiocontrol arising directly from the hydrogen back-transfer has also been advantageously applied starting from secondary allylic alcohols. These alcohols are non-substituted at the alkene end (terminal alkenes) and, consequently, the 1,4-addition step cannot be enantiocontrolling in these processes, which therefore rely on the hydrogen back-transfer.

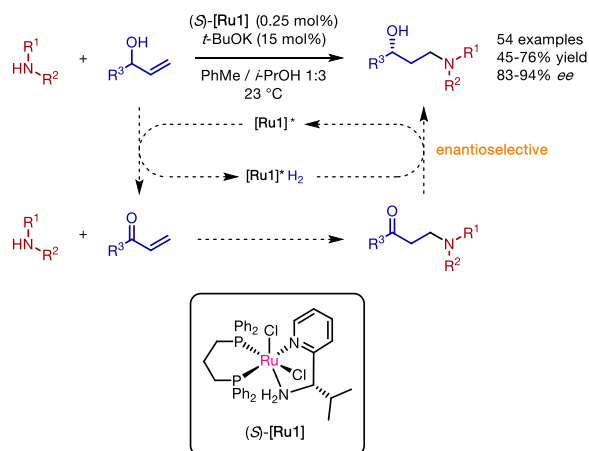
In 2020, Wang and co-workers devised a condensation between amines and racemic allylic alcohols through a 1,4-aza-addition on the intermediate enone (Scheme 27).³⁹ The catalytic cycle starts by the ruthenium-catalyzed dehydrogenation of the initial secondary alcohol, generating the metal hydrogen complex and the reactive enone. The addition of the amine is base-catalyzed, and the process tolerates a wide variety of amines from cyclic ones to acyclic secondary and primary amines. From the formed ketone, the hydrogen back-transfer terminates the catalytic cycle by generating the secondary alcohol product. Using a Noyori-type chiral ruthenium complex (*R,R*)-[**Ru3**], this hydrogen back-transfer occurs with up to 99% *ee*.

While BH *N*-alkylation usually occurs at high temperatures – as in the previously mentioned allylic alcohol functionalizations – here, the reaction can be run at 30 °C, providing excellent levels of enantiocontrol. Useful 1,3-amino-alcohols are easily generated from widely available substrates through such a condensation.



Scheme 27. Enantioselective hydroamination of allylic alcohols.

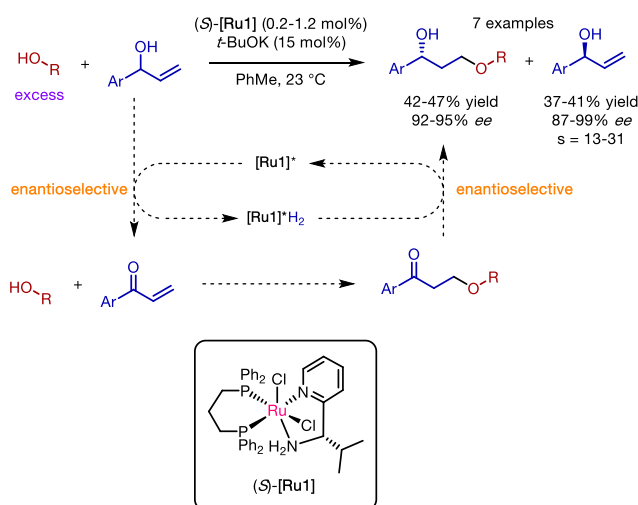
The same year, Jin, Xing and co-workers also developed the same reaction by using another type of chiral ruthenium complex (*S*)-[**Ru1**] (Scheme 28).⁴⁰ This one features an achiral diphosphine (dppp) on one side and a chiral picolylamine ligand on the other one. Consequently, a large variety of amino-alcohols could be formed in up to 94% *ee*. It should be pointed out that isopropanol had to be used as co-solvent in this reaction, acting as an additional hydride donor in the final hydrogen transfer.



Scheme 28. Enantioselective hydroamination of allylic alcohols employing a simpler ruthenium complex.

The same year, Yu, Xing and co-workers extended this type of formal nucleophilic addition on allylic alcohols to the use of primary alcohols as nucleophiles (Scheme 29).⁴¹ While carefully optimizing this reaction, they discovered that the racemic alcohol was kinetically resolved through this process. Indeed, one of the enantiomers of the secondary alcohol reacted faster than the other one in the initial dehydrogenation by a chiral ruthenium complex (s factor typically around 15), providing the slowly reacting allylic alcohol with 87-96% *ee* when an aromatic substituent is present. Continuing the borrowing hydrogen catalytic cycle, the formed enone reacts in a base-catalyzed 1,4-addition, followed by ruthenium-catalyzed enantioselective hydrogen back-transfer to create γ -functionalized alcohols in typically >90% *ee*. Importantly, it was ultimately also shown that the same mechanism of initial kinetic resolution of the starting alcohol was occurring in the previously mentioned aza-Michael addition.

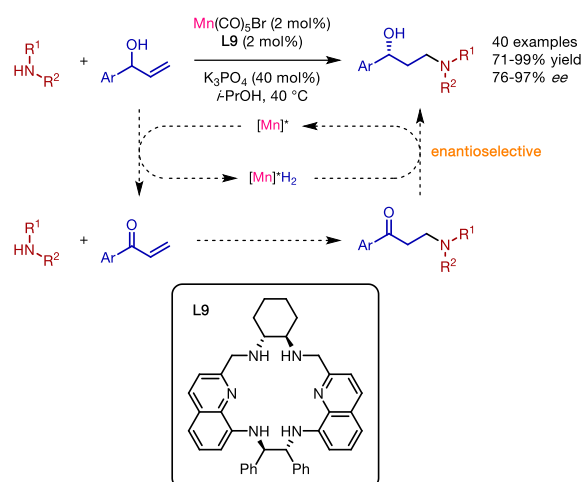
Interestingly, this is an example of a transformation where two independent enantioccontrolling events can occur through a single catalytic cycle, even though, concerning the borrowing hydrogen in itself, only the hydrogen back-transfer is controlling the stereochemistry of the functionalized product.



Scheme 29. Enantioselective functionalization and concomitant kinetic resolution of racemic allylic alcohols.

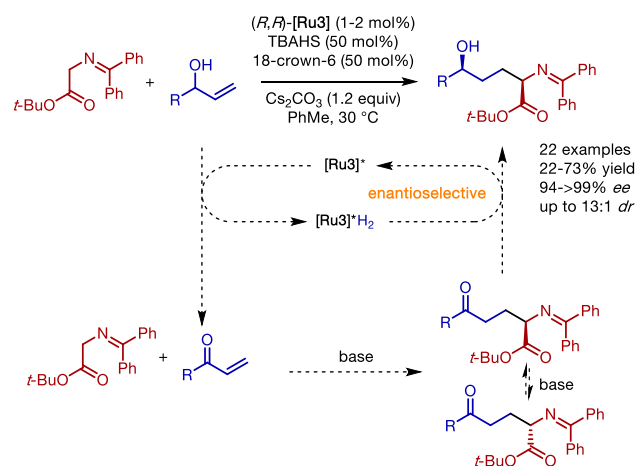
In 2022, an alternative to the use of expensive metals such as the previously disclosed ruthenium complexes was found by the teams of Chen and Fan (Scheme 30).⁴² Key to the development of this reaction was the discovery of a manganese complex incorporating a chiral macrocyclic ligand. This chiral ligand embeds four secondary amines and two quinolines for optimal coordination of manganese carbonyl. Once again, isopropanol is used as a solvent, which might help in the final hydrogenation. Through the precisely

generated metal cavity, the amino-alcohols are obtained in up to 97% *ee*. As a result, this study demonstrates the great potential of alternative complexes based on less expensive metals for efficient enantioselective borrowing hydrogen transformations.



Scheme 30. Enantioselective hydroamination of allylic alcohols using a chiral manganese complex.

Finally, the stereocontrol over the hydrogen back-transfer during allylic alcohol functionalization was extended to controlling two distant stereogenic centers (Scheme 31).⁴³ This reaction is based on the condensation of glycine-derived Schiff base nucleophiles with allylic alcohols.



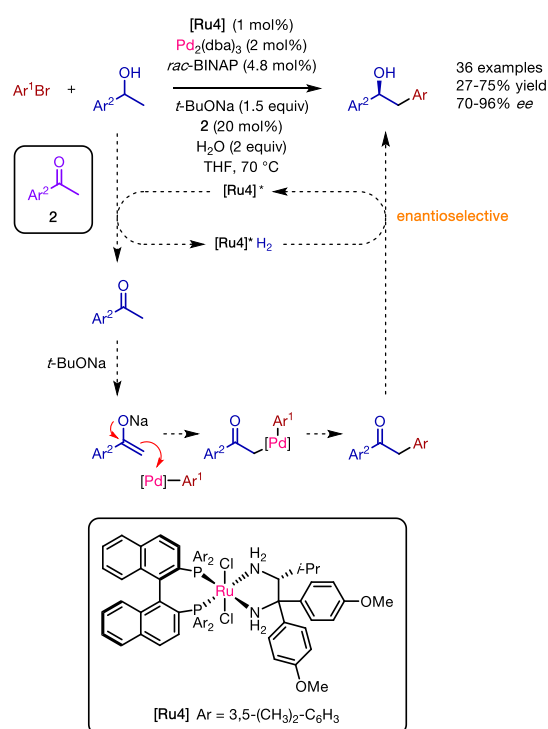
Scheme 31. Enantioselective functionalization of allylic alcohols controlling two distant stereocenters.

Starting from the racemic allylic alcohols, initial dehydrogenation by the metal provides the reactive enone that condenses with the nucleophile through achiral phase transfer catalysis. An enantioselective hydrogen back-transfer from the chiral ruthenium catalyst on the resulting racemic Michael adduct occurs preferentially on one enantiomer. Since the two enantiomers of the Michael adduct can interconvert

through a base-induced racemization, this Dynamic Kinetic Asymmetric Transformation affords the final alcohols with excellent di- and enantio-control (up to 13:1 *dr* and >99% *ee*).

4.4. β -Functionalization of Alcohols

Related to the previous reactions, the last transformation developed concerned the β -functionalization of alcohols with aromatic partners (Scheme 32).⁴⁴ Based on a racemic version initially disclosed by Dydio,¹⁵ the team of Wang developed in 2023, an original multicatalytic combination of an achiral palladium complex and a chiral ruthenium catalyst to perform this type of reaction in an enantioselective manner. The dehydrogenation of the racemic alcohol forms the ruthenium-hydrogen complex and the reactive ketone. Palladium catalyzed α -arylation of the ketone generates the functionalized achiral ketone intermediate. Finally, enantioselective hydrogen back-transfer from chiral the ruthenium catalyst generates the secondary alcohol products in up to 96% *ee*. As a limitation to this system, it was found that a small amount of the ketone corresponding to the secondary alcohol substrate (20 mol%) is required to facilitate the hydrogen transfer during the initial oxidation.



Scheme 32. Enantioselective β -functionalization of alcohols.

Curiously, this kind of approach has been poorly studied and numerous related reactions could be developed in the future following this principle of co-catalyzed β -functionalization of alcohols.

5 Conclusions and Perspectives

Borrowing hydrogen is one of the most elegant manners to directly functionalize alcohols while avoiding waste, additional steps and the cost associated with adjusting the redox state for the functionalization of carbon chains. While borrowing hydrogen transformations are of great synthetic interest, it was only since 2013 that it appeared as a general strategy to create enantioenriched molecules. Since then, the field has seen a great expansion with numerous different approaches developed to control chirality. It is now a general method to generate useful enantioenriched molecules featuring alcohols or amines.

While the most common approach for controlling the absolute stereochemistry remains the hydrogen back-transfer from chiral metal complexes to pro-chiral unsaturated species, other strategies have been developed relying on the enantiocontrol during the functionalization of the intermediate carbonyl by a second catalyst, or less commonly, through an initial enantioselective dehydrogenation.

While the last decade has seen an explosion in the number of disclosed enantioselective borrowing hydrogen transformations, there is plenty of room to improve the existing approaches and develop new ones. This will require the identification of more efficient catalyst structures and original strategies.

-Concerning the classical enantioselective amine alkylation using secondary alcohols, one of the main challenges lies in the high temperatures (typically above 100 °C), required for such transformations, ultimately affecting the capacity of chiral catalysts to control the enantioselectivity. Despite the application of the principles of multicatalysis to improve reaction efficiency, many cases remain where the enantiocontrol is still far from optimum.

-One of the general challenges that borrowing hydrogen faces is also the difficulty at trapping the intermediate carbonyl compounds formed in small amounts within the metal catalytic cycle. While once again multicatalysis has been shown to be an efficient approach to tackle this issue, the identification of other coupling partners would be of great interest.

-As already mentioned, some mechanistic aspects have been poorly studied, and their elucidation would allow to devise many different transformations following those principles, for example through other multicatalytic functionalization of the intermediate carbonyl compound.

-Enantioselective borrowing hydrogen reactions most of the time still rely on the use of metal complexes

based on rare and expensive metals such as iridium or ruthenium. Less expensive metal sources such as iron or manganese have been shown to be of great potential in a limited number of reactions and the future should see a growth in their application. The possibility of development of transition metal-free enantioselective borrowing hydrogen reactions would be of great importance, taking this field one step further in terms of eco-compatibility.

-Finally, in order to induce other types of functionalization of the intermediate carbonyl compound, researchers could advantageously explore the combination of metal-catalyzed borrowing hydrogen and photo- or electro-catalysis.

We hope that this review will inspire the scientific community to tackle the challenges of enantioselective borrowing hydrogen and explore new horizons within this still emerging field.

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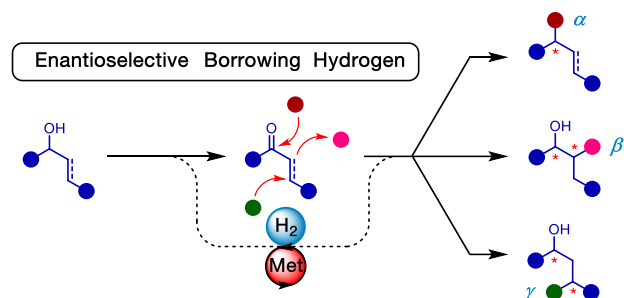
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Enantioselective Borrowing Hydrogen: A Modern Tool for Constructing Enantioenriched Molecules

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Borrowing hydrogen is a crucial approach in order to directly functionalize alcohols through reversible hydrogen transfer reactions. Through the appropriate implementation of chiral catalysts, the last decade has seen the development of enantioselective versions of these eco-compatible transformations. This review presents the principles behind these strategies that can provide a direct access to synthetically important enantioenriched scaffolds.