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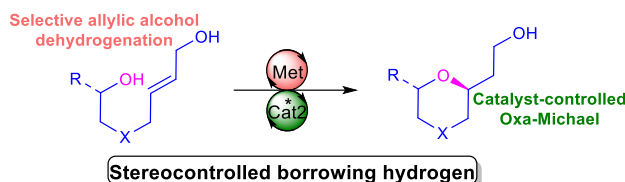
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Iron- and Organo-Catalyzed Borrowing Hydrogen for the Stereoselective Construction of Tetrahydropyrans

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ABSTRACT: Stereocontrolled oxa-Michael additions are challenging given the high reversibility of the process, which ultimately leads to racemization of the newly formed stereocenters. By combining an iron-catalyzed borrowing hydrogen from allylic alcohols with a stereocontrolled organocatalytic oxa-Michael addition, a wide array of chiral tetrahydropyrans were efficiently prepared. The reaction could be performed in a diastereoselective manner from pre-existing stereocenters or enantioselectively from achiral substrates. Key to success was the reactivity of the iron complex, which was selective for the allylic alcohol dehydrogenation and irreversibly led the reaction to the final product.

Borrowing Hydrogen (BH) enables, through the reversible metal-catalyzed transient formation of reactive carbonyl compounds, the direct functionalization of alcohols into more elaborate compounds.¹ Such reactivity has been known for more than a century and is of clear synthetic interest given the considerable synthetic economies it provides (steps, waste...). However, it was only in 2013-2014 that the first efficient enantioselective borrowing hydrogen transformations were reported.² Since then, intense research efforts have led to valuable developments resulting in the efficient construction of different useful scaffolds, such as chiral amines, alcohols, or amino-alcohols.³ Among the methods to control the stereochemistry of BH, starting from allylic alcohols enables to functionalize *in-situ* the intermediate α,β -unsaturated compounds, from which a co-catalyst enables control of the stereoselectivity of the nucleophilic addition (Scheme 1.a). This has been applied to condense, on allylic alcohols, different carbon-nucleophiles such as keto-esters, diketones, aryl boronic acids, ketimine-esters or Schiff bases.⁴ In sharp contrast, when heteroatom nucleophiles such as alcohols or amines are used, the above approach could not be applied to control the stereochemistry of the 1,4-addition. As a result, the main BH strategies for the functionalization of allylic alcohols by heteroatom nucleophiles rely on the use of secondary allylic alcohols possessing a terminal alkene. In this case, the stereocontrol over the BH process lies in the hydrogen back-transfer from the chiral metal complex (Scheme 1.b).⁵ In addition, concerning the potential oxygen nucleophiles, a limited set of non-substituted alcohols (methanol, ethanol and benzyl alcohol) had to be used in large excess, probably due to competing dehydrogenation with the secondary allylic alcohols.

The lack of BH methods allowing for a stereoselective oxa- or aza-Michael addition on the intermediate α,β -unsaturated compounds, is probably due to the difficulty at controlling the stereochemistry of such addition, with the oxa-Michael reaction being especially prone to retro-1,4-addition, thus leading to a fast racemization.⁶

In this context, we hypothesized that both an iron catalyst for the reversible dehydrogenation, and an iminium-type organocatalysis, for a stereoselective oxa-Michael addition, could be associated to perform the stereoselective functionalization of allylic alcohols with alcohol nucleophiles (Scheme 1.c) in a multicatalytic combination.⁷ This strategy could be applied to an intramolecular cyclization, directly providing useful tetrahydropyran derivatives.

However, several key issues and challenges needed to be addressed in order to develop such a stereoselective reaction:

-First of all, in order to generate the reactive enal, the metal complex should selectively dehydrogenate the primary allylic alcohol over the other alcohol. Most notably, starting from a secondary benzylic alcohol as the pro-nucleophile, the competing dehydrogenation of this alcohol could divert the iron catalyst from the required reactivity at the allylic alcohol, or induce a potential racemization of the pre-existing stereocenter.

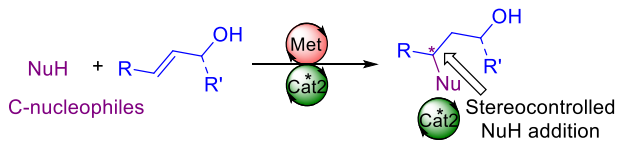
-From the small amount of enal generated upon dehydrogenation of the allylic alcohol by the metal catalyst, the secondary amine organocatalysts should rapidly form the reactive iminium ion. This activated intermediate should then undergo the stereoselective addition of the alcohol. While

such intramolecular additions on aldehydes have been reported,⁶ it was found that the high reversibility of this step leads to the epimerization of the generated stereocenter within minutes.^{6b} In addition, the kinetic of the iminium-catalyzed addition should override the uncatalyzed background oxa-Michael addition, possible at the relatively elevated temperatures required for a borrowing hydrogen.

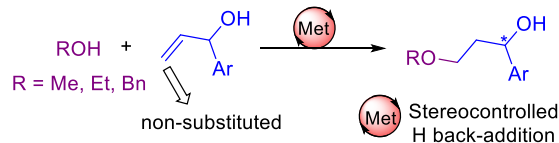
-Finally, in order to prevent the reversibility of the oxa-Michael addition, the hydrogen back-transfer to the functionalized aldehyde should occur both rapidly and irreversibly.

Herein, we report the development of such a multicyclic borrowing hydrogen. This approach can be applied in a diastereoselective process, when starting from enantioenriched secondary alcohols, or in an enantioselective version from racemic or achiral starting materials.

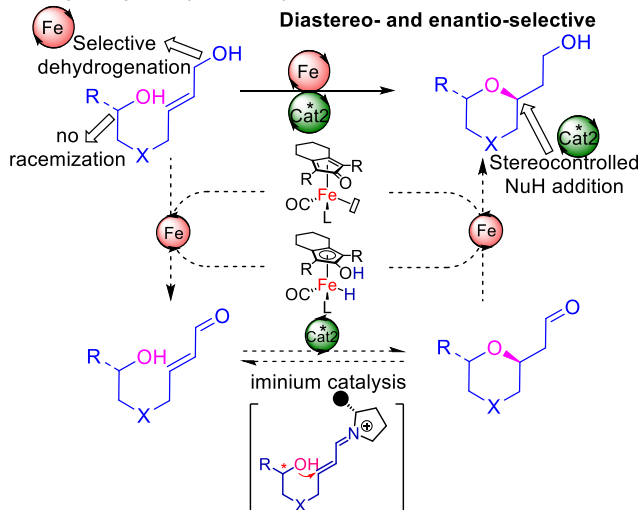
a) Stereocontrolled addition of C-nucleophiles to allylic alcohols:



b) Hydrogen back transfer stereocontrol in allylic alcohols functionalization with alcohols:



c) Multicatalytic borrowing hydrogen synthesis of tetrahydropyrans (this work):

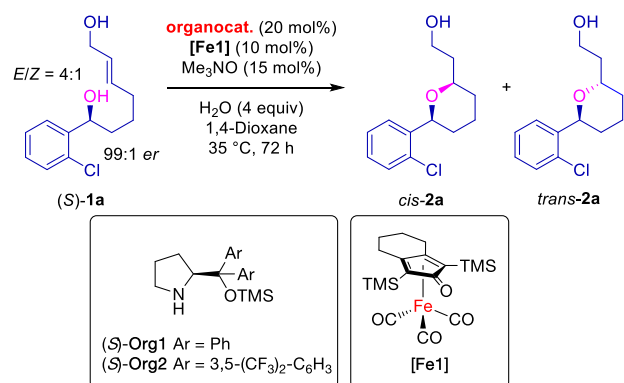


Scheme 1. Literature overview of current allylic alcohols functionalization by BH and this work.

In order to develop this reaction, we first focused on the transformation of enantioenriched diol (*S*)-**1a** (99:1 *er*), featuring a secondary benzylic alcohol and a primary allylic alcohol (Table 1). We used iron complex **[Fe1]** for the borrowing hydrogen, generating the active dehydrogenation catalyst upon nucleophilic abstraction of a CO ligand by Me₃NO.⁸ In the absence of any organocatalyst, the resulting tetrahydropyran was formed with a moderate 20% NMR yield (Entry 1). In addition, *cis*-THP *cis-2a* was generated with modest diastereocontrol (4:1 *dr*). Adding 20 mol%

pyrrolidine provided the same results (Entry 2). Turning to the use of (*S*)-**Org1** as co-catalyst dramatically improved the efficiency of the reaction (Entry 3). Indeed, the reactivity was significantly increased (83 % NMR yield) together with the selectivity (26:1 *dr*), indicating that the organocatalyst considerably accelerated the oxa-Michael addition, which in turn, drove the overall BH process to completion. Altogether, upon purification, this led to the isolation of 66% of *cis-2a* in 34:1 *dr*. Importantly, *cis-2a* was isolated in >99:1 *er*, confirming the absence of racemization of the sensitive stereogenic benzylic alcohol center. (*S*)-**Org2** provided a similar reactivity in the process with a slightly decreased diastereocontrol (19:1 *dr*, Entry 4).

Table 1. Reaction screening in the multicatalytic diol functionalization



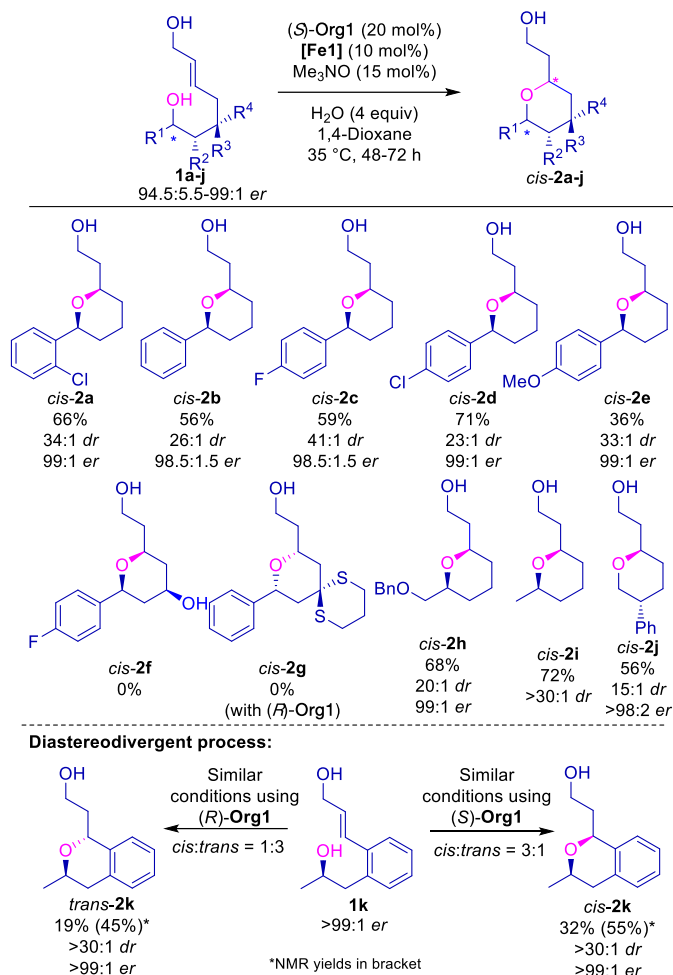
Entry	Organocat.	Conv ^[a]	<i>cis/trans</i> (<i>er cis</i>)
1	none	20%	4 : 1
2	pyrrolidine	25%	4 : 1
3	(S)-Org1	83% (66%) ^[b]	26 : 1 (>99:1 <i>er</i>)
4	(S)-Org2	89%	19 : 1
5	(R)-Org1	63%	2 : 1 (>99:1 <i>er</i>)
6 ^[c]	(S)-Org1	75%	18:1

^[a] Conversion for THP estimated from the ¹H NMR ratio of products to starting material. ^[b] Isolated yield (34:1 *dr*, >99:1 *er*). ^[c] Reaction performed in toluene.

Using the enantiomeric (*R*)-**Org1**, confirmed the role of the organocatalyst over the control of the newly formed stereogenic center. Indeed, using this enantiomer of the catalyst, the yield decreased and most importantly, the product was obtained in only 2:1 *dr* (Entry 5). This confirms that *cis-2a* is generated through a kinetically-controlled stereoselective addition of the alcohol on the iminium ion, and not through a subsequent equilibration to the more favored *cis*-THP, which had previously been observed in iminium-catalyzed processes.^{6g} In this context, (*S*)-**1a** and (*S*)-**Org1** represent the match combination. Finally, the use of toluene, a common solvent for borrowing hydrogen instead of 1,4-dioxane slightly reduced the *dr* to 18:1 (Entry 6). Control ex-

periments indicated that the initial *E/Z* mixture of allylic alcohols converged through a common (*E*)- α,β -unsaturated aldehyde.⁹ Indeed, starting from the allylic alcohol with different *E/Z* composition provided the same results for the formation of *cis*-**2a** (see Supporting Information).

Using this organocatalytic combination, a broad array of enantioenriched diols were readily converted to the corresponding tetrahydropyrans (Scheme 2).



Scheme 2. Scope of the diastereoselective multicyclic diol functionalization (isolated yields and *dr* of the isolated products)

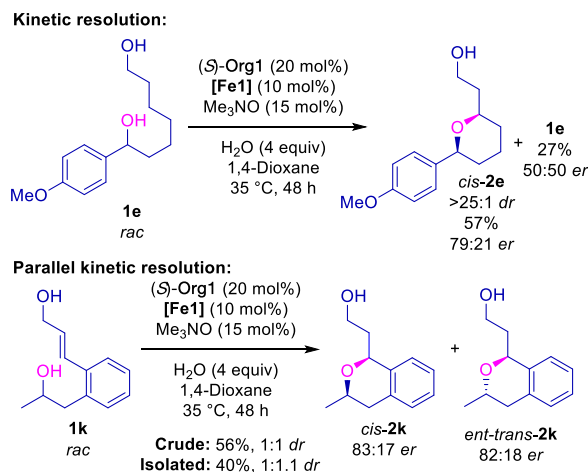
Most notably, the reaction tolerated a broad range of benzylic alcohols **1a-e**, featuring different substitution patterns. With electron-neutral or electron-poor aromatics, the combination of [Fe1] and (*S*)-Org1 provided the expected products **2a-2d** with 56-71% yield and 23:1 to 41:1 *dr*. Importantly, these products were formed in 98.5:1.5-99:1 *er* from initial substrates with 97.5:2.5-99:1 *er*. This confirms the absence of racemization at the benzylic alcohol and an enantioenrichment through the organocatalytic step. The substrate **1e**, possessing an electron-rich aromatic substituent, afforded tetrahydropyran **2e** with excellent diastereoselectivity, albeit in a lower yield, as a consequence of a partial oxidation of the more easily oxidized benzylic alcohol (the corresponding ketone could be isolated in 10% yield). **2e** is generated in 99:1 *er* from **1e** with 95.5:4.5 *er*. This indicates that this oxidation is poorly reversible under the re-

action conditions¹⁰ and confirms once again the enantioenrichment through the oxa-Michael addition. **1f** and **1g**, possessing an additional alcohol or a dithiane did not convert to the corresponding products, possibly through irreversible coordination and deactivation of the iron complex.

Aside from benzylic alcohols containing substrates, other diols were compatible with the multicyclic transformation. Notably, aliphatic secondary alcohols **1h-j**, bearing different functionalities, were efficiently converted to **2h-j** in 68-73% yield with >20:1 *dr*. Absence of racemization was confirmed in **2h**, which was obtained in 99:1 *er* from a 99:1 *er* starting alcohol. Finally, **1j**, possessing two primary alcohols, could also selectively undergo the cyclization to **2j** with equal efficiency.

We finally focused on the preparation of isochromans where the transition state of the oxa-Michael addition would less be subject from the bias of the pre-existing stereocenter. Applying the multicyclic conditions led to a diastereodivergent process, where the two diastereomers of the isochroman **2k** can be accessed from the same enantiomer of the starting diol by simply changing the enantiomer of the organocatalyst. Through the kinetic control of the oxa-Michael addition by the organocatalyst, both diastereomers were formed in 3:1 *dr*, with 19-32% yield of the isolated pure diastereomer.

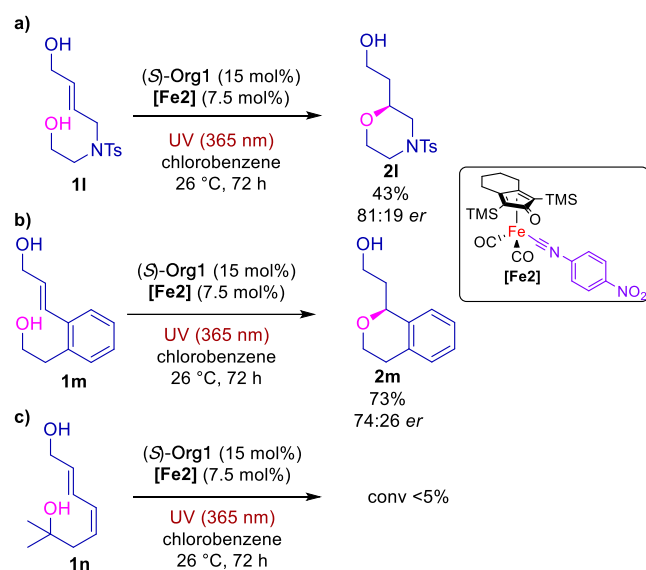
From these diastereoselective processes, we next turned our attention to the development of a kinetic resolution using racemic substrates (Scheme 3). From racemic **1e**, *cis*-**2e** was formed in 57% yield, >25:1 *dr* and 79:21 *er*. This product is observed, together with 27% of the racemic starting material and some oxidation products, confirming the resolution at the oxa-Michael level together with a partial degradation of the slowly reacting intermediate enantiomeric aldehyde. When starting from racemic **1k**, a parallel kinetic resolution occurs, where the two enantiomers react with the same kinetics to provide different products, leading to a 1:1 mixture of *cis*- and *ent-trans*-**2k** in 83:17 and 82:18 *er* respectively. Altogether, these results confirm the stereoselective control over the cyclization by the organocatalyst.



Scheme 3. Kinetic resolution of racemic diols

Given the observation of an enantioselection process in the above-mentioned reactions, we finally turned our attention to the development of an enantioselective transformation

starting from achiral diols **1l-m** featuring a primary alcohol pro-nucleophile (Scheme 4). Experiments conducted using conditions similar to the ones used above notably chemical activation of the iron complex by Me₃NO, failed to provide the expected products with good reactivity (5-19% yield).¹¹ With these substrates, we hypothesized, that Me₃N (generated upon activation of the iron complex), could favor the equilibrium towards the enal, which had already been observed with tertiary amines in oxa-Michael cyclizations with stoichiometric aldehydes.^{6b} In order to avoid this issue, we turned our attention to the photoactivation of the iron complex.¹² Gratifyingly, while **[Fe1]** provided a moderate 14% yield (see SI), applying our recently developed isonitrile-ligated iron complex **[Fe2]**,¹³ activated in a more efficient manner by light, **1l-m** were converted to tetrahydropyrans **2l-m** in 43-73% yield and 74:26-81:19 *er* (Scheme 4). In sharp contrast, regardless of the conditions (chemical or photoactivation), **1n**, featuring a tertiary alcohol, did not react in the multicatalytic process.



Scheme 4. Enantioselective multicatalytic cyclization

With a clear vision of the stereoselection process through secondary amine organocatalysis, in order to better apprehend the borrowing hydrogen reactivity aspect, additional mechanistic control experiments were performed, shedding light on the properties of the iron complex (see Supporting information for the complete catalytic cycle). Notably, dehydrogenation competition experiments of different alcohols were performed in the presence of acetone as a hydride acceptor (see SI). These experiments confirmed that, using iron-cyclopentadienone complex, allylic-alcohols were dehydrogenated much faster than primary or secondary benzylic alcohols, as well as aliphatic ones. This also confirms that, in the borrowing hydrogen, the equilibrium is strongly displaced towards the final aliphatic alcohol, preventing the undesired retro-oxa-Michael pathway, which would be detrimental for the stereocontrol of the process.

To conclude, by appropriately merging iron- and organo-catalysis, a borrowing hydrogen was combined with a challenging stereocontrolled oxa-Michael addition in a multicat-

alytic process to generate functionalize chiral tetrahydropyrans. Through the selective dehydrogenation of the allylic alcohol, by the iron complex, this transformation can be performed in a diastereoselective manner from enantioenriched benzylic alcohols. The organocatalyst controls the stereoselectivity of the oxa-Michael addition in this process, allowing for an extension to the kinetic resolution of racemic diol substrates, or an enantioselective version when starting from achiral diols. Importantly, the hydrogen back-transfer generating the final aliphatic alcohol prevents the stereocenter racemization through a retro-oxa-Michael at the aldehyde level. This discovery should pave the way for the development of other transformations where the BH would prevent the racemization of unstable intermediates.

ASSOCIATED CONTENT

Data Availability Statement. The data underlying this study are available in the published article and its Supporting Information.

Supporting Information. Optimization details, complete experimental procedures, product characterization, additional mechanistic experiments, NMR spectra and chiral chromatograms, this material is available free of charge via the Internet at <http://pubs.acs.org>.

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