Dual Catalysis

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An Iron/Amine-Catalyzed Cascade Process for the Enantioselective Functionalization of Allylic Alcohols**

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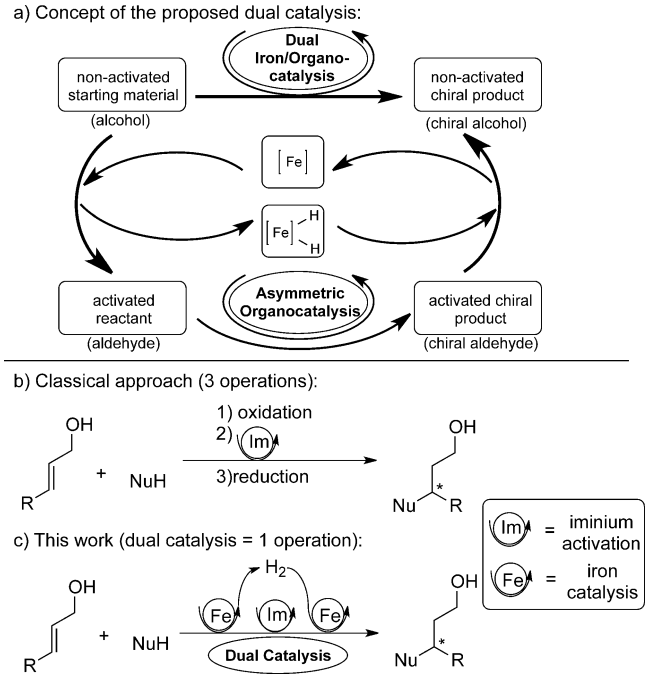
The development of transformations that allow the fast and environmentally compatible generation of enantiopure complex products directly from simple and readily available starting materials is at the forefront of modern synthetic chemistry, and it entails a strong potential for industrial developments.[1] To achieve these ambitious goals, mainly asymmetric transformations that are catalyzed by a single catalyst have been realized, but more recently, the development of multicatalytic approaches has allowed access to new chemical transformations that are otherwise difficult or even impossible to accomplish.[2]

In this context, we intended to combine a hydrogen autotransfer process with an organocatalytic cycle in a dual manner (Scheme 1a). As a result, the reactive carbonyl functionality that is required for an enantioselective aminocatalyzed process would be catalytically generated from the alcohol oxidation level (an unactivated functional group), and then transformed in situ. The strategy should rely on the use of a metal catalyst that is suitable for borrowing-hydrogen processes; if possible, this catalyst should be based on cheap and abundant iron,[3] and it should catalytically and reversibly enable hydrogen transfer without the requirement for a stoichiometric redox reagent.[4] The proposed one-pot relay cascade would be a fully atom-economic and waste-free transformation of simple allylic alcohols into β-chiral saturated alcohols (Scheme 1c), as this process would bypass the three distinct waste-producing steps that are otherwise required (oxidation, organocatalytic nucleophilic addition, reduction; Scheme 1b).

Recently, hydrogen-transfer processes that are promoted by well-defined metal catalysts have been extensively studied, which led to the development of several applications, including hydrogen production or storage and the development of more sustainable chemical transformations.[4] Indeed, these catalysts may induce the transient formation of reactive intermediates from unactivated substrates, and they have thus been applied for so-called borrowing-hydrogen methods. To



Scheme 1. Concept of the dual iron-/organocatalyzed process and its application to the asymmetric functionalization of allylic alcohols.

date, such processes remain largely limited to a small set of reactions, such as alcohol amination or racemic C–C bond-formation,[5] as exemplified by an early example of allylic alcohol substitution, which was reported by Williams and coworkers in 2001.[5d] Unfortunately, the need for relatively harsh reactions conditions (> 70 °C)[6] hampers the development of enantioselective versions of this reaction.[7]

In sharp contrast, chiral iminium activation has established itself as a cornerstone of organocatalytic Michael additions to unsaturated carbonyl compounds, as it enables efficient access to enantiopure complex products.[8] Pivotal to this reactivity is the use of highly reactive carbonyl substrates, namely ketones or aldehydes, that entail severe drawbacks, such as tedious substrate preparation, toxicity, or possible decomposition or product racemization. To avoid such issues, the combination of the in situ formation of the carbonyl functional group with an aminocatalytic step is a promising approach.[9]

Furthermore, we anticipated that combining the two orthogonal catalytic cycles (iminium activation and borrowing-hydrogen catalysis) would enhance the hydrogen-transfer activity of easily accessible iron complexes. A directed thermodynamic displacement by catalytic in situ formation of a chiral conjugated iminium intermediate followed by

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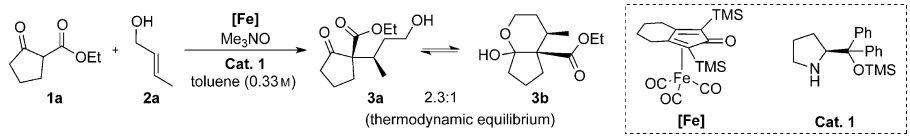
Michael addition and reduction by reversible hydrogen transfer, should lead to a catalytic asymmetric and environmentally friendly process. Herein, we disclose the development of this conceptually new compatible bi-catalytic system that was applied to the asymmetric functionalization of simple allylic alcohols.

To realize this process, methods that enable reversible hydrogen transfer at temperatures suitable for the enantioselective organocatalytic addition step (not higher than RT) had to be used. Borrowing-hydrogen reactions are generally accomplished with precious-metal complexes (Ru, Ir, or Rh) at temperatures where a typical organocatalytic reaction would lack enantiocontrol.[4] On the other hand, the Knölker complex (**[Fe]**; Table 1) has recently emerged as a potentially powerful metal complex for transfer hydrogenation.[10] Given its apparent excellent reactivity, easy preparation, and wide substrate tolerance, we wondered whether this catalyst could be suitable for the designed borrowing-hydrogen process.

For proof of concept, we first focused on the use of carbon-centered nucleophiles (Table 1). Initial experiments indicated that diethyl malonate was a too weak nucleophile for such a reaction.[11] Gratifyingly, after turning to the more nucleophilic ketoester **1a**,[12] crotyl alcohol (**2a**) was efficiently converted into enantioenriched **3**, which was obtained as a thermodynamic mixture of its open and closed forms. A promising 64% yield of the isolated major diastereomer (Table 1, entry 1) was obtained in the presence of the **[Fe]** complex and the aminocatalyst **Cat. 1**,[13] thus validating our initial hypothesis. Furthermore, the product, which bears two contiguous stereocenters, one of them quaternary, was obtained with 80:20 d.r. and 89:11 e.r.

Table 1: Optimization of the reaction conditions: selected results.[a]



Entry	*t* [h]	*T* [°C]	**[Fe]** [mol%]	Me_3NO [mol%]	**Cat. 1** [mol%]	Conv. (Yield)[b] [%]	d.r.[c]	e.r.[d]
1	14	RT	5	10	10	>90 (64)	80:20	89:11
2	20	RT	5	10	10	89 (45)	81:19	91.5:8.5
3	20	RT	5	10	10	71 (51)	82:18	91:9
4	18	RT	5	10	10	64 (35)	82:18	91:9
5	**18**	**RT**	**6.5**	**8**	**13**	**>90 (57)**	**81:19**	**93:7**
6	22	RT	6.5	8	6.5	90 (54)	80:20	91:9
7	23	RT	6.5	8	3	88 (54)	81:19	87.5:12.5
8[e]	16	RT	6.5	8	13	73 (29)	74:26	91.5:8.5
9	38	10	6.5	8	13	51 (nd)	79:21	nd
10	26	10	10	11	20	61(35)	79:21	95:5
11	**51**	**10**	**10**	**11**	**20**	**86 (44)**	**79:21**	**95:5**
12	51	10	2×5	2×5.5	20	74 (nd)	79:21	nd

[a] Reaction conditions: **1a** (0.3 mol), **2a** (1.5 equiv); except for entry 1: **2a** (4 equiv), entry 2: **2a** (2 equiv), and entry 4: **2a** (1.1 equiv). [b] Conversion determined by ^1H NMR spectroscopy. The yield of the isolated major diastereomer is given in parentheses. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] For the determination of the e.r. value, see the Supporting Information. [e] NMO (4-methylmorpholine *N*-oxide) was used instead of Me_3NO. nd = not determined.

With these preliminary results in hand, we then tried to improve the reaction efficiency.[14] Interestingly, the amount of crotyl alcohol could be decreased to 1.5 or even 1.1 equiv without loss of reactivity; the enantioselectivity, however, increased to 91:9 e.r. (Table 1, entries 2–4). More importantly, the catalyst loadings had a strong impact on the overall reaction outcome. At room temperature, the use of **[Fe]** (6.5 mol%) and **Cat. 1** (13 mol%) gave the product in 57% yield and 93:7 e.r. (Table 1, entry 5). Changing the **[Fe]/Cat. 1** ratio to 1:1 or 2.1:1 did not have an impact on the reactivity, but led to a slight decrease in enantiocontrol (Table 1, entries 6,7). Using 4-methylmorpholine *N*-oxide (NMO) instead of Me_3NO to generate the active iron complex (see below), did not lead to a change in the reaction outcome, indicating that this crucial initiation step does not exert an influence on the catalytic cycle (Table 1, entry 8). Lowering the temperature to 10°C increased the enantioselectivity to 95:5 e.r., but a slightly higher catalyst loading and a prolonged reaction time were then required to obtain satisfying reactivity (Table 1, entries 9–11).

With these two sets of optimized conditions in hand (Table 1, entries 5 and 11), we then investigated whether this concept could be extended to a broader family of substrates (Scheme 2). With either method A or B, a wide array of enantioenriched products could be prepared from cyclic or acyclic ketoesters under mild conditions. The enantiomeric ratios ranged from 89.5:10.5 to 95:5 e.r.; in some cases, up to three contiguous stereocenters were controlled with a d.r. value of >9:1. In general, a methyl substituent on the allylic alcohol was well-tolerated, and so were an *n*-propyl moiety or a hydrogen atom at this position. The use of allyl alcohol ($R^4 = H$) is particularly interesting, as it corresponds to a formal addition to acrolein without having to handle this toxic compound.

Aside from alkyl-substituted allylic alcohols, in a preliminary experiment with cinnamyl alcohol (**2d**), lactol **12** was obtained in 63% yield, 93:7 e.r., and >9:1 d.r. (Scheme 3a). The overall process may also be scaled up; by using only 1 mol% of **[Fe]** and 2 mol% of **Cat. 1**, lactol **7** was obtained in 91:9 e.r. from 5 mmol of starting material (Scheme 3b). Furthermore, the lactols **9** and **10**, which were obtained by addition to crotyl alcohol (**2a**), could be derivatized, for example, by alcohol dehydration (Scheme 3c) or protection (Supporting Information), which highlights the synthetic potential of the process.

Control experiments were conducted to shed light on the reaction mechanism (Scheme 4). When one of the components (**[Fe]**, Me_3NO, or **Cat. 1**) was removed from the

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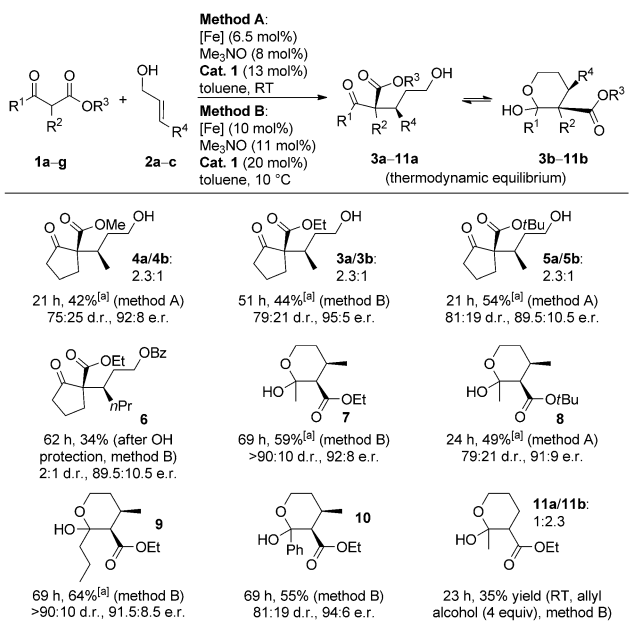
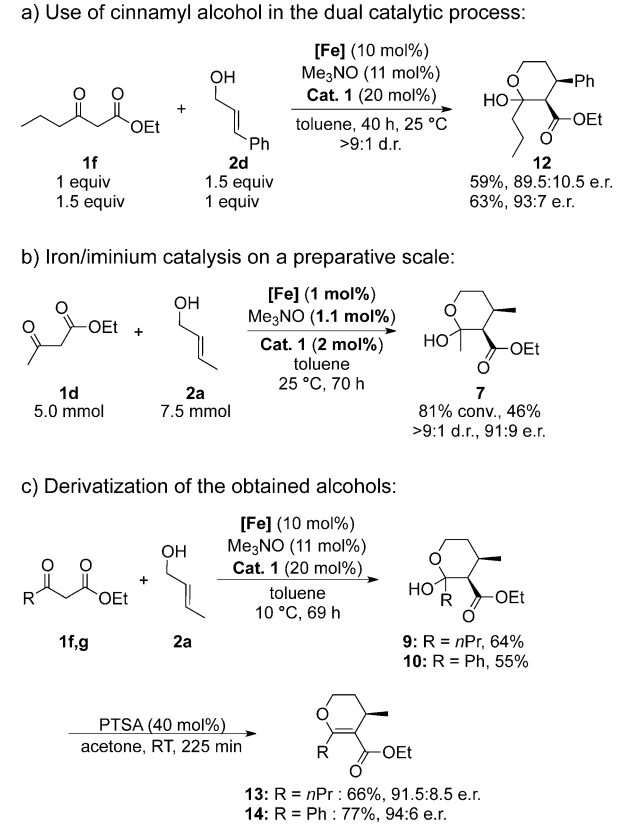
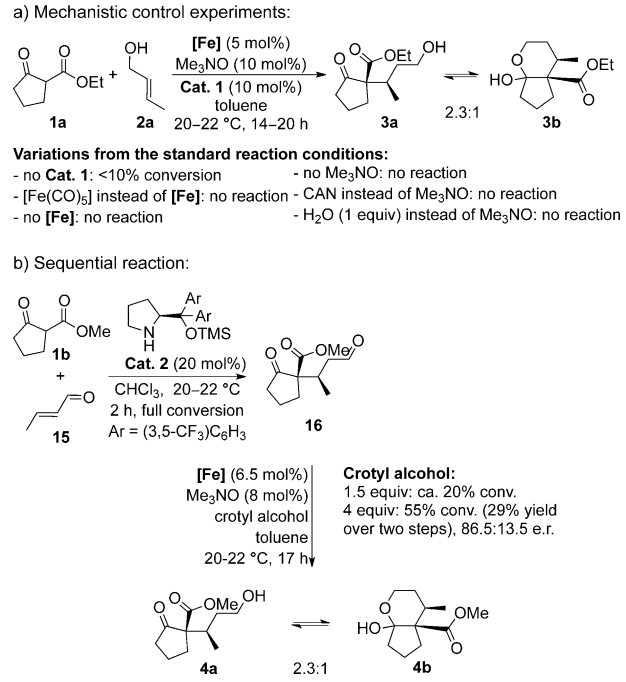


Scheme 2. Scope of the dual iron/amine-catalyzed process. [a] The yield of the isolated major diastereomer is given.



Scheme 3. Application of cinnamyl alcohol as a substrate for the cascade reaction, reaction scale-up, and lactol derivatization. PTSA = toluene-*p*-sulfonic acid.

mixture, no reaction was observed, which confirms the synergistic effect between the active iron complex and the aminocatalyst (Scheme 4a). When Me_3NO was replaced by ceric ammonium nitrate (CAN) or water as the initiating



Scheme 4. Mechanistic experiments.

reagent, the active iron complex was not generated, which resulted in a complete loss of reactivity. Finally, the Knölker-complex precursor $[Fe(CO)_5]$ did not promote the reaction, which confirms the nature of the active species. All of these observations support the involvement of a borrowing-hydrogen process combined with an organocatalytic cycle. Additional insights into the mechanism were gained by performing a sequential process: The previously reported Michael addition on crotonaldehyde (**15**) with **Cat. 2**[12c] was followed by reduction of the corresponding adduct **16** by **[Fe]**/Me_3NO in the presence of crotyl alcohol as a hydrogen donor (Scheme 4b). Interestingly, only partial conversion to the reduced adducts **4a/b** was observed, even in the presence of a large excess of crotyl alcohol. This clearly suggests a reversible reduction process and corroborates our initial hypothesis on the synergistic role of catalytic iminium activation, as it seems to enhance the activity of the borrowing-hydrogen sequence.

The influence of the iron catalyst loading on the reaction rate and the turnover number (TON) indicates that reversible hydrogen transfer might be the rate-determining step of the system. Indeed, as similar conversions were observed when two amounts of 5 mol% or directly 10 mol% of **[Fe]** were employed, it is likely that at this temperature, the limiting parameter is the turnover frequency (TOF) of the iron catalyst (Table 1, entries 11 and 12). Furthermore, the lower conversion that is observed when the amount of **[Fe]** was decreased suggests that the TON is also determined by the iron complex. This is corroborated by the fast production of the Michael adduct when the addition is directly performed with crotonaldehyde (2 h at RT; Scheme 4b). Finally, when starting from crotyl alcohol (**2a**) or directly from crotonaldehyde (**15**), the same absolute and relative configurations were observed; these results imply that only the iminium-activation

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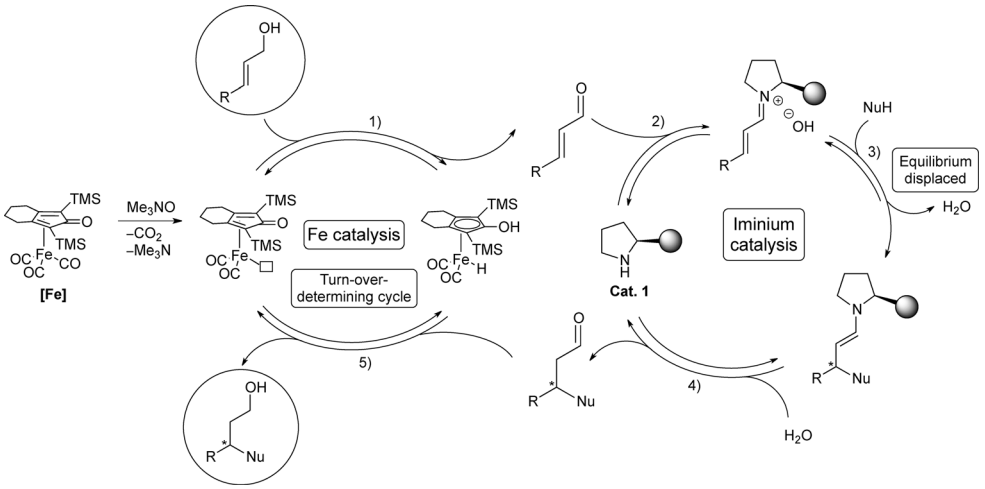

Scheme 5. Proposed mechanism for the iron/amine-catalyzed cascade process. TMS = trimethylsilyl.

mode is involved in the enantiodetermining Michael-addition step.

From all of these experiments, we propose a dual cooperative catalytic cycle (Scheme 5). The reaction is initiated by the formation of an active iron complex that possesses a vacant site, which is obtained by CO decoordination from **[Fe]** with Me_3NO.[15] This complex abstracts hydrogen from the allylic alcohol, which leads to the α,β-unsaturated aldehyde (step 1) that is then able to react in the iminium catalytic cycle (step 2). Enantioselective Michael addition (step 3) displaces the global equilibrium of the transformation to the short-lived β-chiral aldehyde after liberation of aminocatalyst **Cat. 1** (step 4). Chemoselective reduction of this aldehyde (step 5) in the presence of the ketone functional group of the pronucleophile by the transient iron–hydrogen complex finally gives the stable β-chiral alcohol and regenerates the active iron complex. From the mechanistic experiments, it seems that under these conditions, the reaction efficiency in terms of TOF and TON depends on the rate of hydrogen transfer. As a result, research aimed at improving the reactivity of these systems should focus on the design of more reactive and robust iron catalysts.

In conclusion, we have disclosed a conceptually new cooperative iron-catalyzed borrowing-hydrogen/iminium-activation strategy. The resulting bicatalytic system enables the transformation of allylic alcohols into β-chiral alcohols under mild conditions (10 °C–RT) and with high enantioselectivities (up to 95:5 e.r.). Key to success was the insertion of the iminium catalytic cycle into the iron-catalyzed hydrogen autotransfer process. It allows for enantiocontrol and to thermodynamically drive the reaction towards the irreversible formation of the saturated alcohol. Preliminary mechanistic experiments have provided a better understanding of the highly chemoselective catalytic cycle and opened new insights for further developments, especially considering the involvement of unstable aldehyde intermediates. Given the proposed generality of the concept, we are convinced that this preliminary work should open the way for the development of a wide variety of redox-neutral enantioselective transformations of general interest.

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