Kinetic Resolution

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Merging Iron Catalysis and Biocatalysis—Iron Carbonyl Complexes as Efficient Hydrogen Autotransfer Catalysts in Dynamic Kinetic Resolutions

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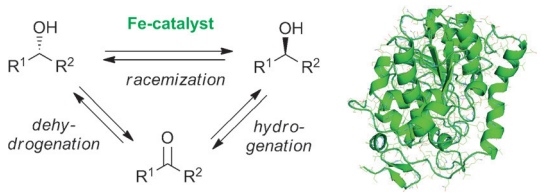
Abstract: *A dual catalytic iron/lipase system has been developed and applied in the dynamic kinetic resolution of benzylic and aliphatic secondary alcohols. A detailed study of the Knölker-type iron complexes demonstrated the hydrogen autotransfer of alcohols to proceed under mild reaction conditions and allowed the combination with the enzymatic resolution. Different racemic alcohols were efficiently converted to chiral acetates in good yields and with excellent enantioselectivities.*

Over the last decades, transition metal catalysis has been further developed and plays a crucial role in the chemical and pharmaceutical industries. Its significance was recognized by three Nobel Prizes for the use of noble metal catalysis in organic synthesis.[1] In recent years, efforts have been made to develop processes that can be catalyzed by more earth-abundant metals including iron.[2]

Enantiomerically pure alcohols and amines are among the important key intermediates used in both academia and industry.[3] The kinetic resolution via either esterification or hydrolysis is one of the most important methods used in industrial production of optically pure alcohols and amines.[4] Its major drawback is the limited yield which cannot exceed 50%. Metal-catalyzed racemization of the slow-reacting enantiomer has emerged as a powerful tool to increase the theoretical yield to 100% via dynamic kinetic resolution (DKR).[5]



Scheme 1. Iron-catalyzed racemization of alcohols for dynamic kinetic resolution with enzymes.

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In an early study, Williams et al. reported the combination of a rhodium(II)acetate dimer and lipase to achieve the DKR of 1-phenylethanol.[6] The groups of Bäckvall, Kim, and Park have pioneered the concept of ruthenium-catalyzed racemization of alcohols and amines via either reversible transfer hydrogenation or β-hydride elimination.[7] The relatively high cost and limited availability of ruthenium-based racemization catalysts have triggered the development of more cost-effective and readily accessible metal catalysts. For instance, Berkessel et al. have developed an $AlMe_3$/binol/lipase system to catalyze the DKR of secondary alcohols. In this case the corresponding enol acetates have to be used as the acylating agent which may limit the practicality of this protocol.[8] Furthermore, Akai et al. have reported highly efficient cooperative vanadium/lipase systems for deracemization. This method is limited to allylic alcohols. Moreover, heterogeneous acids have been reported as racemization catalysts.[9] The racemization in these protocols proceeds via a dehydration pathway, which limits the substrate scope to alcohols that can only form a stable carbocation intermediate.[10] Despite these advances, DKR protocols with alternative cheap, readily available, and efficient catalysts would be highly desirable.

Inspired by nature and the fact that the Fe-hydrogenases catalyze the reversible heterolytic cleavage of hydrogen,[11] we decided to investigate iron-based catalysts. These iron catalysts must fulfil the requirements of both enzyme compatibility and redox activity (Scheme 1). Therefore the use of an efficient and compatible iron dehydrogenation–hydrogenation catalyst would be key to the development of such a dual enzyme and iron catalysis protocol.

The iron-catalyzed hydrogenation was reported by Casey and Guan.[12] They employed the bifunctional Knölker complex **8** for the reduction of carbonyl compounds.[13] Beller and co-workers combined the iron-based catalyst **8** and Brønsted acids for the enantioselective reduction of C=N bonds whereas, Quintard and Rodriguez realized the combination of iron complex **1** with iminium catalysis for the functionalization of primary allylic alcohols.[14] Taking into account the recent advances in iron cyclopentadienone catalysis,[15] we here report our preliminary results on the iron-catalyzed dehydrogenation–hydrogenation of secondary alcohols and the challenging combination with biocatalysis.

We began our studies with the racemization of (*R*)-1-phenylethanol [(*R*)-**10a**] and tested several tricarbonyl iron complexes bearing different innocent ligands **1**–**6** (Figure 1). The precatalysts were activated in situ by partial oxidative decarbonylation with trimethylamine *N*-oxide (Me_3NO). Unfortunately, they did not show high catalytic activity and no complete racemization was realized even after prolonged

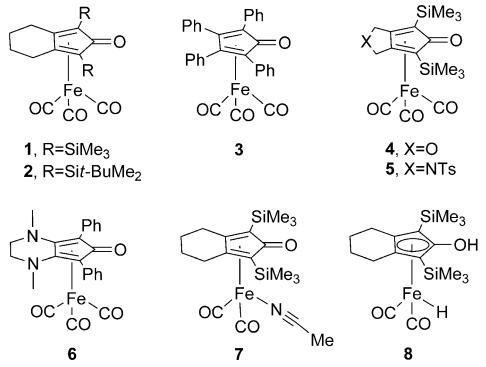
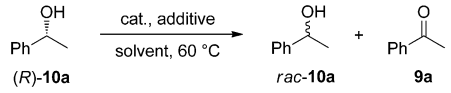


Figure 1. Iron complexes used in this study.

Table 1: Iron-catalyzed racemization of (*R*)-1-phenylethanol [(*R*)-**10a**].[a]



(*R*)-**10a** *rac*-**10a** **9a**

Entry	Cat. (mol%)	Additiev (mol%)	*rac*-**10a**/**9a**[b]	*t* [h]	*ee* [%][b]
1	**1** (10)	Me_3NO (15)	91:09	18	93
2	**2** (10)	Me_3NO (15)	84:16	18	86
3	**3** (10)	Me_3NO (15)	90:10	18	36
4	**4** (10)	Me_3NO (15)	83:17	18	18
5	**5** (10)	Me_3NO (15)	83:17	18	13
6	**6** (10)	Me_3NO (15)	83:17	18	41
7	**7** (10)	–	92:08	18	56
8	**8** (10)	–	77:23	6	0
9	**8** (5)	–	80:20	9	0
10	**8** (10)	**9a** (20)	87:13	5	0
11[c]	**8** (10)	–	78:22	8	0
12[d]	**8** (10)	–	80:20	7	0
13[e]	**8** (10)	–	91:09	18	26
14[f]	**8** (10)	–	80:20	5	0

[a] The reactions were performed on a 0.2 mmol scale with the iron complex and additive in 1 mL of toluene at 60 °C in a Schlenk tube under an inert atmosphere. [b] The ratios of products and *ee* of **10a** were determined by gas chromatography using a β-dex column. [c] Benzene as the solvent. [d] Cyclohexane as the solvent. [e] *tert*-Butanol as the solvent. [f] *n*-Hexane as the solvent.

heating (Table 1, entries 1–6). This is in agreement with Funk and Moyer's observation of catalyst poisoning during the oxidation of alcohols.[15d]

We then turned our attention to the use of the mono-acetonitrile dicarbonyl analogue, which also did not fully racemize the alcohol (*R*)-**10a** even after 18 hours (Table 1, entry 7). Interestingly when we used the isolated air-sensitive iron hydride complex **8**, complete racemization was realized after only 6 hours in toluene at 60 °C (Table 1, entry 8). Reducing the catalyst loading to 5 mol% increased the reaction time to 9 hours (Table 1, entry 9), while the presence of 20 mol% of acetophenone enhanced the reaction rate and the racemate was formed after only 5 hours (Table 1, entry 10). The racemization could also be carried out in several nonpolar solvents but the racemization rate slowed down in the polar protic *tert*-butanol and 26% *ee* was detected after 18 hours (Table 1, entries 11–14). The racemization was

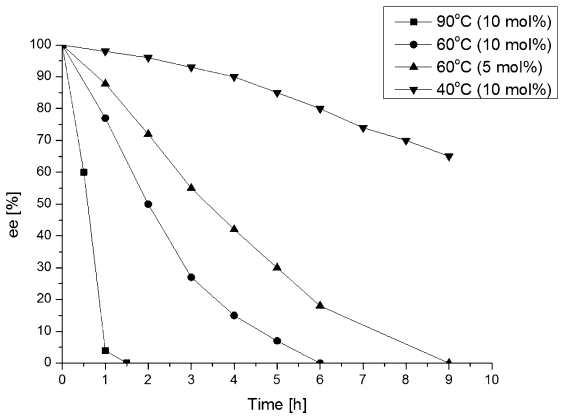
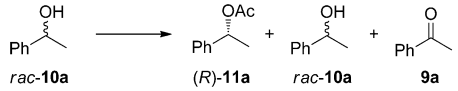


Figure 2. Reaction profile of the racemization of (*R*)-**10a** (0.2 M) using iron complex **8**.

found to be highly dependent on temperature. While only 90 minutes at 90 °C and 6 hours at 60 °C suffice for complete racemization, we observed lower reactivity at 40 °C (Figure 2).

With the good racemization catalyst **8** in hand we decided to combine the iron-catalyzed dehydrogenation–hydrogenation sequence with the enzyme-catalyzed resolution via acetylation using lipase from *Candida antarctica*. This enzyme typically shows good thermostability and activity. After reaction optimization complete conversion of the *rac*-**10a** was obtained when vinyl acetate or isopropenyl acetate was employed as the acyl donor (Table 2, entries 1 and 2).

Table 2: Iron/enzyme-catalyzed DKR of *rac*-**10a**.[a]



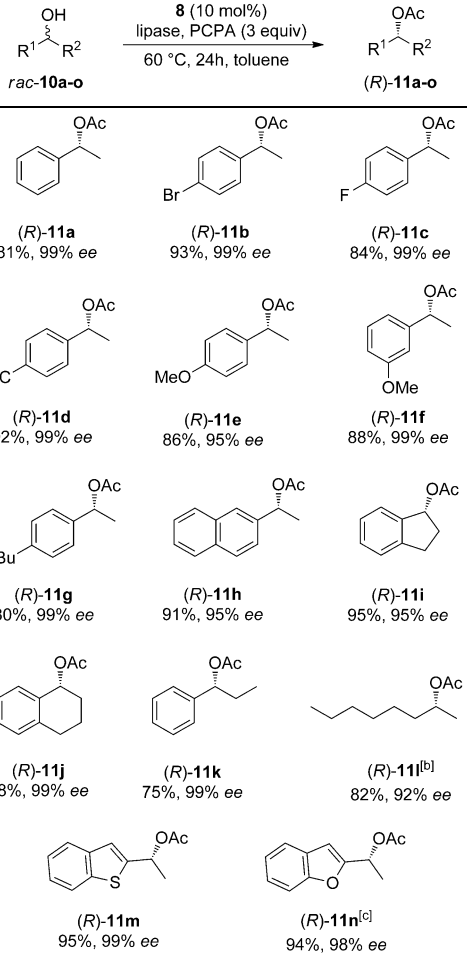
rac-**10a** (*R*)-**11a** *rac*-**10a** **9a**

Entry	Acetylating reagent	**11a**/**10a**/**9a**[b]	*ee*[b] [%]
1	vinyl acetate	56:0:44	99
2	isopropyl acetate	72:0:38	99
3	1-ethoxyvinyl acetate	80:20:0	74
4	acetyl isopropyl carbonate	64:26:10	34
5	*p*-chlorophenyl acetate (PCPA)	100:0:0	99

[a] The reactions were performed on a 0.2 mmol scale with iron complex **8**, 3 mg of Novozyme-435, and 3 equiv of acyl donor in 1 mL of toluene at 60 °C for 18 h in a Schlenk tube under an inert atmosphere. [b] The ratios of products and *ee* of **11a** were determined by gas chromatography with a β-dex column.

However, despite high stereocontrol, the formation of considerable amounts of acetophenone **9a** was observed which can be explained by the generation of the hydrogen acceptors acetaldehyde or acetone. To overcome this limitation, we used 1-ethoxyvinyl acetate which produces ethyl acetate as a byproduct. Unfortunately, only 80% yield and 74% *ee* resulted (Table 2, entry 3). The reaction with acetyl isopropyl carbonate showed also lower reactivity and selectivity (Table 2, entry 4). Importantly, *p*-chlorophenyl acetate (PCPA) was found to be compatible for the iron- and enzyme-catalyzed DKR of alcohols (Table 2, entry 5).

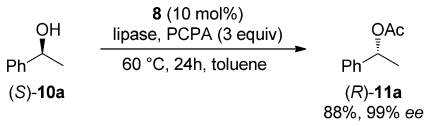
Table 3: Reaction scope for the iron/lipase-catalyzed DKR.[a]



[a] Reaction conditions: **10** (1 mmol), catalyst **8** (10 mol%), Novozyme-435 (15 mg), and PCPA (3 mmol) in toluene (5 mL) were stirred at 60 °C for 24 h in a Schlenk tube under an inert atmosphere; yields after column chromatography. *ee* values were determined by GC with β-dex columns. [b] Toluene (2.5 mL). [c] Novozyme-435 (10 mg).

To demonstrate the potential and applicability of this methodology, an array of racemic secondary alcohols were resolved by the iron/enzyme system (Table 3). We initially explored the alcohols known to be suitable for DKR with enzymes.[4c–f] 1-Phenylethanol (**10a**) afforded the corresponding acetate **11a** in 81% yield with 99% *ee*. Use of electron-deficient alcohols (**10c–e**) provided the corresponding acetates in good yields and excellent enantioselectivities. However, for the substrate with a 4-methoxy substituent a slight decrease of the enantiocontrol was observed, while the reaction rate and enantioselectivity did not change significantly for the 3-methoxy and the 4-alkyl derivatives (**10e–g**). Also, the DKR of the 1-naphthyl derivative **10h** proceeds well. Furthermore, indanol **10i** underwent the DKR with good yield (95%) and good *ee* (95%), whereas the acetate **11j** was obtained in only 68% yield along with the corresponding ketone. Importantly, the aliphatic alcohol 2-octanol (**10l**) was transformed into the desired acetate in good yield and high optical purity. Additionally, different heterocyclic derivatives (**11m** and **11n**) could also be applied successfully.

Next, we investigated the inversion of configuration by employing (*S*)-**10a** under the optimized reaction conditions. Pleasingly, the reaction proceeds with complete inversion of configuration to give the acetate (*R*)-**10a** in 88% yield and 99% *ee* (Scheme 2). Thus the procedure may be a good alternative to the Mitsunobu reaction which is often applied for inversion of chiral alcohols in organic synthesis.



Scheme 2. Iron/enzyme-catalyzed inversion of (*S*)-**10a**.

In conclusion, we have developed the first example of a cooperative nonnatural iron/lipase catalytic system.[16] The key to success is the unprecedented combination and compatibility of a reactive iron dehydrogenation–hydrogenation catalyst with a lipase. The iron-catalyzed hydrogen autotransfer proceeds under very mild reaction conditions which facilitates the combination with the enzyme. Various racemic alcohols including benzylic, aliphatic, and heteroaromatic alcohols have been transformed into the enantioenriched acetates without the use of precious metal catalysts and expensive chiral ligands. Given the compatibility of iron catalysis with enzymatic resolutions demonstrated here and the fact that the iron catalyst is inexpensive and readily available, we believe that these initial promising findings will open up new avenues for further exploration of this effective dual catalysis system.

Keywords: chiral alcohols · hydrogenases · kinetic resolution · lipases · reduction

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