Chemoenzymatic Dynamic Kinetic Asymmetric Transformations of β-Hydroxyketones

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Abstract: Herein we report on the development and application of chemoenzymatic Dynamic Kinetic Asymmetric Transformation (DYKAT) of β-substituted β-hydroxyketones (β-HKs), using Candida antarctica lipase B (CALB) as transesterification catalyst and a ruthenium complex as epimerization catalyst. An operationally simple protocol allows for an efficient preparation of highly enantiomerically enriched α-substituted β-oxoacetates. The products were obtained in yields up to 95% with good diastereomeric ratios.

Asymmetric synthesis remains an important part of organic chemistry, strongly impacting other scientific areas.[1] Various areas of chemical industry have a stable growing demand of optically pure compounds,[2] with the resolution of racemic mixtures still being the preferred method industrially.[3] Ever since the possibility to combine enzymes and transition metals in one-pot procedures was reported,[4] considerable efforts into combining enzymes and transition metals in catalytic systems have been undertaken.[5] Development of systems combining in situ transition metal-catalyzed racemization with enzymatic kinetic resolution (KR) has resulted in so-called dynamic kinetic resolution (DKR), efficiently solving racemic mixtures of e.g. sec-alcohols in theoretically quantitative yields,[6] providing convenient access to valuable functionalized alcohols.[7] Further, chemoenzymatic D KR procedures have been successfully applied in the resolution of α-hydroxyketones or the asymmetric syntheses of diaryl diols.[8] Recently, also systems using organocatalysis or photocatalysis cooperatively with enzyme catalysis or bi-enzymatical DKR systems have been developed[9] and applied.[10] Chemoenzymatic DYKAT[10] protocols have been developed for the diastereo- and enantioselective transformations of diastereomeric mixtures of diols[11] and found application in the synthesis of enantiomerically pure 1,3-diol monoacetates (Scheme 1a). We have previously developed a DYKAT of 1,3-diols to access enantiomerically pure syn-1,3-diacetates combining enzymatic resolution and Ru-catalyzed epimerization additionally including intramolecular acyl migration in 1,3-syn-diol monoacetates (Scheme 1a). Another example includes preparation of γ-hydroxyketones from 1,4-diols that takes advantage of a facile dehydrogenation step when employing Ru-complex Ia together with an acyl donor affording γ-oxoacetates as products (Scheme 1b).

Scheme 1. Examples of previously reported methods for DYKAT of diols and this work.

To date various metal-based racemization catalysts have been reported to be compatible with enzyme catalysis, including ruthenium-based complexes. Early D KR systems employed a combination of lipase CALB and Shvo’s catalyst (la).[12] Park and co-workers later introduced a new type of RuCl-complexes with superior racemization properties.[13] The Bäckvall group developed a highly potent RuCl-complex (III), which has since then found application in various D KR and DYKAT systems.[14a-d] With the latter catalyst racemization of 1-phenylethanol takes place at room temperature in minutes.[14a,b] Further, this catalyst system suppresses the commonly occurring side reaction of substrate oxidation, which is a common problem with the early D KR systems employing catalyst la.[6a]

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Chiral β-hydroxyketones (β-HKs) are commonly found in nature,[15,16] for example as pheromone components of Sitona and Sitophilus weevils.[15a–g] In addition, β-HKs constitute a class of valuable building blocks, commonly employed in the total synthesis of natural products, i.e. polyketides.[16] We envisioned an effective epimerization mechanism for α-substituted β-hydroxyketones 1 with RuCl-complex II (Scheme 2a), including a [1,5]-migration of ruthenium hydride species ([Ru]-H) between the oxygen atoms of the 1,3-diketone moiety in intermediates int-A and int-B as the key step (Scheme 2b). The transformation is proposed to proceed via a non-chiral intermediate int-C. It has been previously demonstrated during mechanistic studies on the racemization of sec-alcohols with RuCl-complex II that the substrate does not leave the coordination sphere of the metal during the oxidation-reduction process.[17] In contrast, the use of Ru-complex I under analogous reaction conditions would lead to an equilibrium where the 1,3-diketone would readily dissociate from the corresponding [Ru]-H moiety, which would in turn lead to oxidation of the substrate.[18] Furthermore, an expected reaction rate difference between the enzymatic acylation of syn- and anti-diastereoisomers of α-substituted β-HKs would lead to formation of highly useful diastereomerically enriched β-oxoacetates as products.

We postulated that an increase of the steric demand of the substituent in the α-position of the β-HKs would lead to improved diastereoselectivity of the overall process. Initial attempts to obtain a DYKAT of β-HKs indicated a significant drop in the rate of the enzymatic acylation when α-substituted 3-hydroxy-5-heptanones were used as substrates compared to that of 2-hydroxy-4-pentanones. Hence, β-HK 1a bearing a benzyl substituent in the α-position was chosen as the standard substrate in the optimization of the reaction conditions (Table 1).

Initially experiments were conducted employing Ru-complex 1a as the racemization catalyst. p-Chlorophenyl acetate was chosen as the acyl donor due to the observed increased formation of the undesired diketone 3a when acyl donors such as vinyl acetates were employed. An enzyme loading of 80 mg/mmol of lipase CALB was found to be necessary for achieving good yield of the desired product 2a in cyclohexane as the solvent after 20 h at 80°C. The desired β-oxoacetate 2a was formed in 83% yield, with a moderate diastereomeric ratio (dr) with a syn:anti ratio of 30:70 (Table 1, entry 2). High enantiomeric excess (ee) was observed, even though the formation of minor amounts of the undesired enantiomer suggests that epimerization is not sufficiently fast over the whole reaction course. Substrate oxidation to give 3a as a byproduct in small amounts occurred as a result of acceptorless dehydrogenation.

### Table 1. Optimization of the reaction conditions.[a]

| Entry | Ru-cat [mol %] | CALB [mg/mmol] | solvent [M] | 2a [%][b] | 3a [%][b] | syn-2a:anti-2a[c] | ee of anti-2a [%][d] |
|-------|----------------|----------------|-------------|-----------|-----------|-----------------|---------------------|
| 1     | 1a (2.5)       | 40             | CyH (0.2)   | 49        | 8         | 30:70           | 97                  |
| 2     | 1a (2.5)       | 80             | CyH (0.2)   | 83        | 8         | 30:70           | 97                  |
| 3     | 1a (2.5)       | 80             | THF (0.2)   | 39        | –         | 32:68           | 99                  |
| 4     | 1a (2.5)       | 80             | DCE (0.2)   | 27        | –         | 30:70           | 99                  |
| 5     | 1a (2.5)       | 80             | rBuOH (0.2) | 12        | 8         | 23:77           | 99                  |
| 6     | 1a (2.5)       | 80             | PhMe (0.2)  | 85        | 10        | 30:70           | 97                  |
| 7     | 1b (2.5)       | 80             | PhMe (0.2)  | 81        | 5         | 34:66           | 95                  |
| 8     | 1c (2.5)       | 80             | PhMe (0.2)  | 78        | 5         | 38:62           | 95                  |
| 9     | 2 (5.0)[e]     | 40             | PhMe (0.2)  | 88        | –         | 30:70           | 99                  |
| 10    | 2 (5.0)[e]     | 40             | PhMe (0.2)  | 95        | (90)[f]   | –               | 35:65               | 99                  |
| 11    | 2 (5.0)[e]     | –              | PhMe (0.2)  | 88        | –         | 48:52           | 96                  |

[a] Unless otherwise noted reactions were conducted under argon atmosphere in the indicated solvent (1.0 mL) at 80°C using 1a (0.2 mmol), p-CIPhOAc (1.5 equiv), Na2CO3 (1.5 equiv), Ru-cat (2.5–5 mol%), and CALB (indicated amount). [b] Yield determined by 1H NMR using mesitylene as the internal standard. [c] dr and ee determined by GC on chiral stationary phase. [d] Using KOBU (0.1 M solution in toluene, 5 mol%) as an additive. [e] Using isopropanol acetate (1.5 equiv) as the acyl donor. [f] Isolated yield. [g] Using lipase PS-IM (80 mg/mmol) instead of CALB and the reaction time was 64 h. DCE = 1,2-dichloroethane.
of 1a catalyzed by Ru-complex 1a. Use of solvents such as THF, DCE or tBuOH in the reaction led to a considerable decrease of the yield of 2a (Table 1, entries 3–5). Toluene was found to be the best solvent in this transformation (Table 1, entry 6). Screening of other racemization catalysts such as Ru-catalysts Ib and Ic led to decreased yields of 2a, as well as lower ee values (Table 1, entries 7–8).

To further improve the enantioselectivity of the reaction and suppress formation of the undesired oxidation product 3a, RuCl-complex II was tested as a racemization catalyst in this reaction (Table 1, entry 9). Due to the superior epimerization performance of catalyst II, the enzyme loading could be reduced to half while retaining high yield and ee of 2a. The RuCl-complex II was also found to be compatible with isopropenyl acetate as the acyl donor (Table 1, entry 10), which facilitated the product isolation. Under these optimized reaction conditions β-oxoacetate 2a was obtained in 90% isolated yield, 99% ee and a syn:anti ratio of 35:65 with no detected formation of 3a. We also tested the performance of lipase PS-lIM in the DYKAT of 1a (Table 1, entry 11). Under analogous reaction conditions after 64 h reaction time the β-oxoacetate 2a was obtained in 88% yield, albeit with a decrease of both dr and ee.

To gain further insight into the diastereoselectivity of the enzymatic acylation reaction of 1a, the relative rates of the formation of diastereomers syn-1a and anti-1a were measured. First, a parallel experiment was carried out using syn-1a and anti-1a as substrates (Figure 1). In this setting, alcohol anti-1a undergoes acetylation to furnish anti-2a approximately twice as fast as syn-1a.

Additionally, a competitive KR experiment was run, using compound 1a with a starting diastereomeric ratio close to 1:1 syn:anti (Scheme 3). The faster reacting diastereomer preferentially binds to the enzyme and thereby prevents access of the slower reacting diastereomer, potentially amplifying the diastereoselection. The competitive reaction indicates a relative rate difference of 1:3 between syn- and anti-diastereoisomers, based on the observed dr of the product 2a at low conversion.

Next, the scope of the newly developed DYKAT reaction was investigated (Scheme 4). Under the previously established optimal reaction conditions (Conditions A), products 2a–c were obtained in excellent yields, very high enantioselectivity, and moderate dr. However, β-HK 1d with n-butyl substituent in the α-position led to dr of 45:55 (syn:anti) under these reaction conditions. We argued that the rate of enzymatic acylation of 1d is too fast for an efficient epimerization to occur by [1,5]-migration of RuH. Hence, we further investigated if an increased diastereomeric ratio of 2d could be achieved by lowering the enzyme-to-catalyst ratio. After an additional screening of reaction conditions (see the Supporting Information) new optimized reaction conditions were established (Conditions B). We observed that decreasing the amount of enzyme in the reaction decreased the yield and increased the reaction time, whereas raising the amount of ruthenium-catalyst to 7.5 mol% and diluting the reaction mixture resulted in high yield of product 2d with increased dr compared to the reaction with the previously used optimized conditions (Conditions A). The newly optimized reaction conditions (Conditions B) were further applied for substrates 1b, 1c, and 1e in order to achieve higher dr of the corresponding products. Substrate 1f containing a terminal alkene moiety afforded the corresponding β-oxoacetate 2f in 45% yield with moderate dr, but with decreased ee of both diastereoisomers. The yields of acetates 2g and 2h obtained were low due to their instability under the reaction conditions (they readily underwent elimination reactions to form the corresponding α,β-unsaturated ketones as side products). Higher enzyme loading and longer reaction times were necessary to achieve efficient DYKAT of the 3-hydroxy-5-heptanone-derived β-HKS 1i–k in good yields. Surprisingly, α-methyl-substituted β-oxoacetate 2i showed a slight preference for the syn-diastereomer, in contrast to the previous examples described here. A plausible reason for this preference is the way...
that the β-HK adapts to the enzyme pocket, since the methyl substituent is less sterically demanding than the propionyl moiety in 2i. Introducing additional steric hindrance by creating a quaternary stereogenic center in β-HK caused an increased steric demand. Even after prolonged reaction time, β-oxoacetate 2l was obtained in low yield, with just marginally better dr than 2a and decreased ee. Interestingly, cyclic β-HK 1m was also found to be compatible with the newly developed DYKAT protocol and afforded the corresponding β-oxoacetate 2m in 80% yield and dr of 40:60 (syn:anti).

As it was previously demonstrated, Ru-complex 1a can be used to efficiently reduce ketones to alcohols via transfer hydrogenation by the use of an external alcohol as a hydrogen donor.\(^{19}\) Herein we disclose a tandem hydrogenation-DYKAT of 1,3-diketone 3a as a one-pot procedure (Scheme 5). By employing Ru-complex 1a as the racemization/transfer hydrogenation catalyst, the mono reduction of the 1,3-diketone moiety in 3a and the subsequent epimerization and enzymatic acylation of the in situ generated β-HK, afforded the desired β-oxoacetate 2a in 65% NMR-yield with high enantiomeric excess.

In conclusion, we have reported the first protocol for chemoenzymatic DYKAT of α-substituted β-HKs. The newly developed method afforded highly useful β-oxoacetates as products in good yields with high enantioselectivity and moderate diastereoselectivity. The diastereoselectivity of the overall process is proposed to be dependent on the rate difference of the enzymatic acylation of syn- and anti-diastereomers of the β-HK which is largely influenced by the steric demand of the substituent in the α-position. While lipase CALB performed well and afforded moderate to good dr of the target β-oxoacetates, the use of lipase PS-IM led to considerable decrease of the diastereoselectivity of the reaction. We expect, that future improvements in terms of diastereoselectivity can be achieved by the discovery of even more selective lipase enzymes in the near future. A complimentary approach would be to use genetic tools like directed evolution where the enzyme performance could be specifically tailored to the described DYKAT protocol.

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**Conflict of Interest**

The authors declare no conflict of interest.

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