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COMMUNICATION

Efficient dynamic kinetic resolution of racemic secondary alcohols by a chemoenzymatic system using bifunctional iridium complexes with C–N chelate amido ligands†‡

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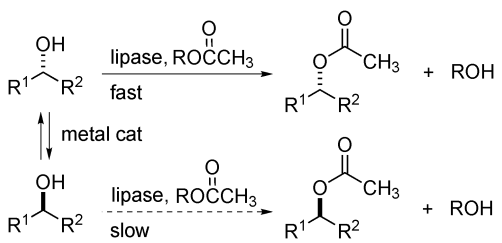
The combined catalyst system of bifunctional amidoiridium complexes derived from benzylic amines with CALB was found to provide a range of chiral acetates from racemic secondary alcohols in excellent yields with nearly perfect enantioselectivities *via* dynamic kinetic resolution.

Synthesis of optically pure secondary alcohols has been one of the promising methods to access chiral building blocks in asymmetric transformations. Among them, kinetic resolution of racemic mixture using enzymes is a traditional and versatile procedure and can be applied to practical processes; however, the maximum yield is inherently limited to 50%.[1] Dynamic kinetic resolution (DKR) including the enzymatic kinetic resolution of racemic alcohols and the *in situ* racemisation of the remaining enantiomer has been regarded as an expedient idea, allowing complete conversion to single enantiomeric compounds as shown in Scheme 1.[2] Since Bäckvall[3] and other groups[4] established DKR systems based on Shvo's complex or the related Ru complexes as racemisation catalysts for secondary alcohols (**1**) and CALB (*Candida antarctica* lipase B immobilised on polyacrylamide; Novozym 435) as a practical biocatalyst for enantioselective transesterification, more efficient racemisation catalysts for alcohols have been extensively explored[5] and their combined use with biocatalysts has been tested in a one-pot synthesis of chiral acetates (**2**).[5a,d–f] To broaden the perspective on chiral technologies involving the chemoenzymatic protocol, there still remains some unsolved drawbacks, low turnover numbers of metal catalysts, relatively high temperature and/or basic conditions required for the racemisation, as well as an excess use of acylating agents.



Scheme 1 DKR of racemic secondary alcohols by combination of metal-catalyzed racemisation with enzymatic transesterification.

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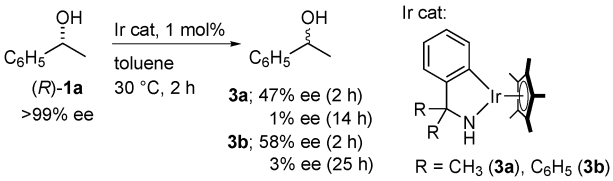
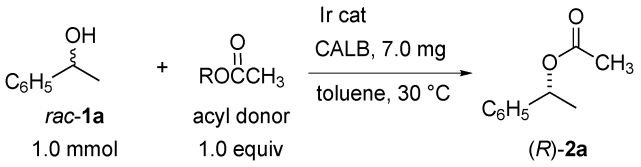
Group 8 and 9 complexes bearing chelate protic amine ligands have also been established as highly effective hydrogen transfer catalysts between alcohols and ketones *via* interconversion between amido and hydrido(amine) complexes based on a metal/NH bifunctionality.[6] Whilst some precursory Ru or Ir complexes derived from achiral amine ligands[7] such as *N*-tosylethylenediamine, diphenylphosphinoethylamine and benzylamine have shown to be effective for racemisation of enantiomerically enriched 1-phenylethanol derivatives, it turns out to be hardly amenable to the DKR process, possibly due to a lack of their compatibility with lipase and acyl donors. We have recently developed a new family of bifunctional amidoiridium complexes, $Cp^*Ir[\kappa^2(N,C)\text{-}(NHCR_2\text{-}2\text{-}C_6H_4)]$ (Cp^* = 1,2,3,4,5-pentamethylcyclopentadienyl; R = CH_3 (**3a**) and C_6H_5, (**3b**)), as highly efficient catalysts for transfer hydrogenation of ketones and aerobic oxidation of alcohols.[8] We envisioned that the catalytic performance of these two complexes can be utilised for the racemisation of secondary alcohols and we found that a chemoenzymatic system including the amido-Ir catalyst and CALB provides an efficient procedure for synthesis of enantiomerically pure acetates from a racemic mixture of secondary alcohols under ambient and neutral conditions.

We initially examined racemisation of (*R*)-1-phenylethanol (**1a**) (>99% ee; 0.5 M in toluene) using 1 mol% of the C–N chelate amidoiridium complexes at 30 °C under an argon atmosphere as illustrated in Scheme 2. After the 2 h reaction with **3a** and **3b**, the optical purities were reduced to 47% and 58% ee, respectively, and **3a** led to complete racemisation within 14 h. This experiment



Scheme 2 Racemisation of (*R*)-1-phenylethanol with bifunctional amidoiridium complexes under neutral conditions.

Table 1 Chemoenzymatic DKR of racemic **1a** using the bifunctional C–N chelate Ir complex and CALB with acyl donors



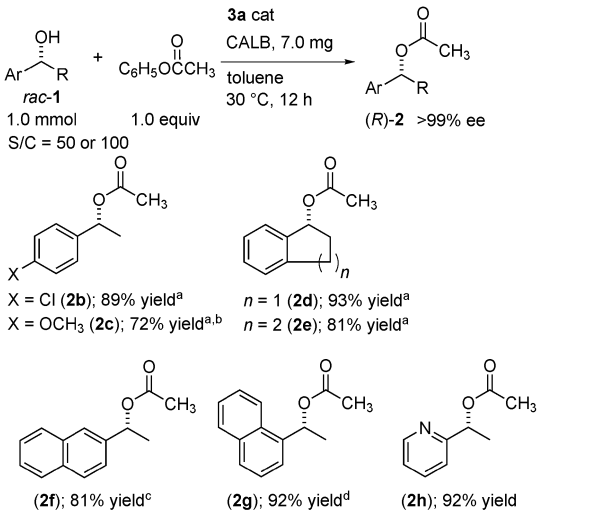
Entry	Ir cat	Acyl donor	S/C	Conc./ M	Time/ h	Yield[a] (%)	ee[b] (%)
1	**3a**	Phenyl acetate	20	0.2	6	88	>99, *R*
2	**3b**	Phenyl acetate	20	0.2	6	81	>99, *R*
3	**4a**[c]	Phenyl acetate	20	0.2	6	70	>99, *R*
4	**4b**[c]	Phenyl acetate	20	0.2	6	69	99, *R*
5	**3a**	Phenyl acetate	30	0.2	6	92	>99, *R*
6	**3a**	Phenyl acetate	100	1.0	12	98	>99, *R*
7	**3a**	1,2-Diacetoxy-benzene	30	0.2	6	68	>99, *R*
8	**3a**	3-Pyridyl acetate	30	0.2	6	52	>99, *R*
9	**3a**	Isopropenyl acetate	30	0.2	6	50	>99, *R*
10	**3a**	1-Ethoxyvinyl acetate	30	0.2	6	25	>99, *R*

[a] Determined by GC analysis. [b] Determined by HPLC. [c] $KO^tC_4H_9$ (6 mol%; 1.2 equiv./Ir) was added.

clearly shows that the coordinatively unsaturated amido complexes exhibit good activities for the racemisation of chiral alcohols even in the absence of base, whereas an addition of $KOC(CH_3)_3$ is required for the analogous C–N chelate amine–Ru and Ir complexes reported by Feringa and de Vries *et al.*[7c,d]

Based on promising catalytic performance of the amido complexes for the racemisation, the DKR of racemic 1-phenylethanol (1 mmol) with an equimolar amount of an acyl donor in toluene (0.2 M) in the presence of the Ir catalyst with a substrate/catalyst ratio (S/C) of 20 and CALB (7 mg) was examined. As listed in Table 1, both amido complexes **3a** and **3b** showed good compatibility with the lipase and phenyl acetate as the acyl donor to afford (*R*)-1-phenylethyl acetate (**2a**) in good yields (88% and 81%) with excellent enantiomeric excesses exceeding 99% after the 6 h reaction at 30 °C (entries 1 and 2). Compared to the direct use of **3**, *in situ* generation of amido-Ir species by treatment of the precursory amine complexes, $Cp^*IrCl[\kappa^2(N,C)\text{-}(NH_2CR_2\text{-}2\text{-}C_6H_4)]$ (R = CH_3, **4a**; C_6H_5, **4b**), with 1.2 equiv. of $KOC(CH_3)_3$ spoiled the reaction, resulting in a lower yield of the ester under otherwise identical conditions (entries 3 and 4). With the superior combination of **3a** with CALB, the amount of Ir catalyst can be diminished (entries 5 and 6). Notably, a desirable yield of 98% with an almost perfect optical purity (>99% ee) was accomplished with a reduced catalyst loading of 1 mol% by increasing the concentration of substrates to 1 M. The possible acceleration of racemisation at a higher concentration of alcoholic substrate may fulfill requirements to enhance the total catalytic activity.

Screening of suitable acyl donor reagents for the DKR system revealed that an almost pure single enantiomer of acetate was produced in all experiments, but catalytic efficacy of **3a** was not observed by use of 1,2-diacetoxybenzene (entry 7). In addition, the DKR system did not accord with 3-pyridyl acetate and enol acetates such as isopropenyl acetate and 1-ethoxyvinyl acetate to give unsatisfactory results (entries 8–10). Thus, phenyl



(a) S/C = 50; (b) 18 h; (c) [**1**] = 0.5 M; (d) 2.0 equiv of phenyl acetate was used.

Scheme 3 DKR of racemic secondary alcohols with the combined catalysts of **1a** with CALB under neutral conditions. Yields were determined after isolation.

acetate was employed as a suitable acylating agent in the following experiments. The concomitantly generated phenol was found to be inert during the reaction.

With the combined catalyst system of **3a** (S/C = 50 or 100) with CALB (7 mg), the DKR of several secondary alcohols was investigated at 30 °C in toluene (1 M) as the standard conditions, and the results are summarised in Scheme 3. In all cases, the *R*-enantiomers with >99% ee were obtained from the reaction under mild conditions. Phenylethanol derivatives (**1b** and **1c**) bearing Cl and OCH_3 substituents on the phenyl ring can be transformed into the corresponding acetates (**2b** and **2c**) with high chemical yields, although a prolonged reaction time of 18 h was needed for **1c** due to a relatively slow rate of racemisation. Chiral acetates (**2d** and **2e**) derived from 1-indanol and 1-tetralol were obtained with comparable results in terms of yield and enantioselectivity. Because of a limited solubility of the 1-(2-naphthyl)ethanol, the DKR was undertaken at a concentration of 0.5 M, and the chiral acetate (**2f**) was obtained in 81% yield. For the sterically congested substrate of 1-(1-naphthyl)ethanol, the racemisation took place as well under the standard conditions but the use of two molar amounts of phenyl acetate was beneficial for a complete conversion into the product (**2g**). Notably, a successful result of an isolated yield of 92% with >99% ee for the pyridine derivative (**2h**) represents an efficient nature of the combined catalyst system.

In summary, we have found that the coordinatively unsaturated amidoiridium complexes **3** behave as racemisation catalysts for secondary alcohols under mild and base-free conditions. Moreover, the well-defined complex **3a** derived from cumylamine proved to be highly effective for the DKR of racemic alcohols by combination with enzymatic transesterification using CALB and phenyl acetate. This chemoenzymatic system is characterised by excellent catalytic performance and operational simplicity. Even at ambient temperature a complete conversion of racemic alcohols is readily attainable using an equimolar amount of acyl donor and no additional bases are needed for racemisation.

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