Asymmetric Catalysis

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Lipase/Aluminum-Catalyzed Dynamic Kinetic Resolution of Secondary Alcohols**

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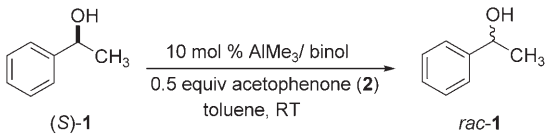
The combination of enzymatic kinetic resolution with a metal-catalyzed racemization by reversible hydrogen transfer was reported by Williams and co-workers for the preparation of enantiomerically pure secondary alcohols. In this early work, the rhodium catalyst $[Rh_2(OAc)_4]$ and a lipase effected dynamic kinetic resolution (DKR) with 60% conversion and 98% *ee*.[1] The research groups of Bäckvall,[2–5] Kim, and Park[6–8] have devised related protocols using ruthenium-based racemization catalysts originally developed by Shvo and Menashe[9] in combination with an immobilized lipase from *Candida antarctica* (CALB, commercially available as Novozym 435). In general, high yields and enantiomeric excesses were obtained. As shown by Jacobs et al., the DKR of secondary benzylic alcohols can also be achieved by combining an acidic zeolite as the racemization catalyst with a lipase in a biphasic system.[10,11]

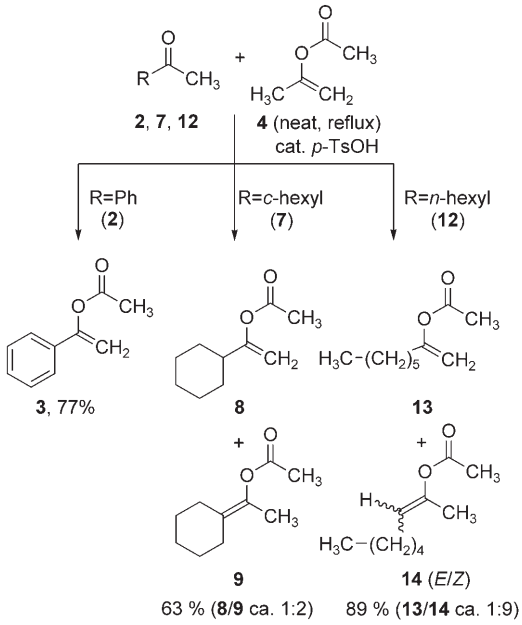
We considered using aluminum-based catalysts, which are easily obtainable and inexpensive. The Meerwein–Ponndorf–Verley–Oppenauer (MPVO) reaction can be exploited for the racemization of alcohols:[1,12–14] Oppenauer oxidation of the alcohol is followed by nonstereoselective reduction of the resulting ketone by the Meerwein–Pondorf–Verley reaction. In general, preformed aluminum alkoxide catalysts such as commercially available $Al(i\text{PrO})_3$ are less active than Ru-based systems.[1] As a consequence, relatively high temperatures and prolonged reaction times are usually required. However, much higher reactivities for MPV reductions have recently been reported for dinuclear Al^{III} complexes[15–17] and for Al^{III} alkoxides generated in situ.[18] With this in mind, we set out to investigate the activity of aluminum alkoxides prepared in situ for the racemization of chiral secondary alcohols and in particular their utility for the DKR of these substrates in the presence of lipases and acylating agents.

We first generated several aluminum species by reaction of $ClAlMe_2$ or $AlMe_3$ with the bidentate ligands (*R*)- and (*S*)-1,1′-bi-2-naphthol (binol), in different ratios, and examined their ability to racemize (*S*)-1-phenylethanol ((*S*)-**1**). Acetophenone (**2**, 0.5 equiv) was employed as a hydrogen acceptor (Scheme 1).



Scheme 1. Racemization of (*S*)-1-phenylethanol ((*S*)-**1**).

$AlMe_3$/binol (1:1) proved to be a very effective catalyst: At room temperature, 10 mol% of the Al catalyst sufficed to racemize the substrate completely within three hours. The aluminum catalysts generated from (*R*)- and (*S*)-binol showed virtually identical activity. On the basis of these findings, we developed a method for the DKR of 1-phenylethanol (*rac*-**1**). We chose 1-phenylvinyl acetate (**3**) as the acylating agent. The commonly used 2-propenyl acetate (**4**) gives acetone as the by-product, which acts as a hydrogen acceptor and oxidizes 1-phenylethanol (**1**) to acetophenone (**2**). 1-Phenylvinyl acetate (**3**) is easily synthesized (Scheme 2; see the Supporting Information for experimental details) from the corresponding ketone, acetophenone (**2**). During the acylation of 1-phenylethanol (**1**) by the enol ester **3**, 1 equivalent of acetophenone (**2**) is released; it does not need to be removed, as it acts as a hydrogen acceptor in the racemization.



Scheme 2. Synthesis of 1-phenylvinyl acetate (**3**), 1-cyclohexylvinyl acetate (**8**) and (1-cyclohexylidene ethyl) acetate (**9**), and 2-(1-octenyl) acetate (**13**) and (*E*/*Z*)-2-(2-octenyl) acetate (**14**). Ts = toluenesulfonyl.

Table 1 summarizes the results of the DKR of 1-phenylethanol (*rac*-**1**) under a range of conditions with Novozym 435 as the lipase. The best results were obtained with binol as the ligand (Table 1, entries 1 and 2). 2,2′-Biphenol showed almost the same activity (entry 3): acetate **5** was obtained in up to 96% yield and 96% *ee*. When phenol was used as the ligand (Table 1, entry 4), significantly lower catalyst activity and lower enantioselectivity resulted. Similarly, the use of the

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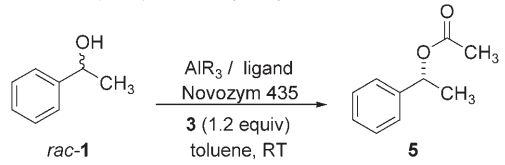
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: DKR of 1-phenylethanol (*rac*-**1**).[a]



rac-**1** → **5**

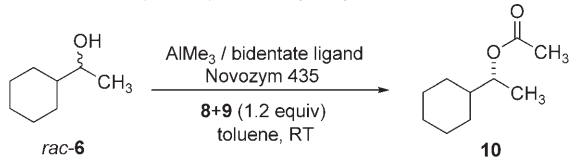
Entry	Ligand (equiv)	AlR_3 (equiv)	*t* [h]	Yield of **5** [%]	*ee* [%]
1	(*R*)-binol (0.1)	$AlMe_3$ (0.1)	3	93	95
2	binol (0.1)	$AlMe_3$ (0.1)	3	96	96
3	2,2′-biphenol (0.1)	$AlMe_3$ (0.1)	3	96	94
4	phenol (0.2)	$AlMe_3$ (0.1)	25	82	85
5	2,5-dimethylhexane-2,5-diol (0.1)	$AlMe_3$ (0.1)	3	51	78
6	binol (0.2)	$AlMe_3$ (0.1)	3	60	95
7	binol (0.05)	$AlMe_3$ (0.1)	3	89	92
8	–	$AlMe_3$ (0.1)	18	84	55
9	–	$AlMe_3$ (0.05)	20	64	74
10[b]	binol (0.1)	$Al(iPrO)_3$ (0.1)	70	94	95

[a] Unless otherwise noted, reactions were run on a 2.5-mmol scale at RT under Ar atmosphere with **3** (1.2 equiv) as the acylating agent and with 12 mg of Novozym per mmol of alcohol. Yields and *ee* values were determined by chiral GC. The configuration of the product ester **5** was assigned by conversion of enantiomerically pure (*S*)-1-phenylethanol ((*S*)-**1**) to the acetate and GC co-injection. [b] Reaction conducted at 60 °C.

aliphatic diol 2,5-dimethylhexane-2,5-diol as the ligand led to unsatisfactory yields and enantiomeric excesses of product **5** (Table 1, entry 5). Apparently, the ligand on Al must be bidentate and of the bisphenol type. When the amount of aromatic bidentate ligand exceeded 1 equivalent relative to aluminum, the activity of the catalyst decreased significantly (Table 1, entry 6). Similarly, when the amount of aluminum exceeded that of the aromatic bidentate ligand, the results obtained were again below optimum (Table 1, entry 7). When the phenolic ligand was omitted completely, the yields and enantiomeric excesses decreased considerably (Table 1, entries 8 and 9). It was interesting to note that even the low activity of commercial $Al(iPrO)_3$ increased upon combination with binol (Table 1, entry 10). Nevertheless, the reaction times were considerably longer and the temperatures higher than those required with the $AlMe_3$-derived catalyst system.

To demonstrate the scope of the DKR process, we tested the aliphatic alcohols 1-cyclohexylethanol (*rac*-**6**) and 2-octanol (*rac*-**11**) as substrates. In both cases, we used "specific" acylating agents that were synthesized from the corresponding ketones cyclohexyl methyl ketone (**7**), and 2-octanone (**12**), respectively (Scheme 2). The racemization of 1-cyclohexylethanol (**6**) turned out to be slower than that of 1-phenylethanol (**1**). However, when longer reaction times and higher amounts of the aluminum catalyst (usually 20 mol %) were applied in the DKR, excellent yields and enantioselectivities were obtained (Table 2). For example, in the presence of 20 mol % of $AlMe_3$/binol (or 2,2′-biphenol), acetate **10** was obtained in virtually quantitative yields and 99 % *ee* (Table 2, entries 1, 2, and 4). Comparable results could be achieved after shorter reaction times when the temperature was increased to 60 °C (Table 2, entry 3).

Table 2: DKR of 1-cyclohexylethanol (*rac*-**6**).[a]



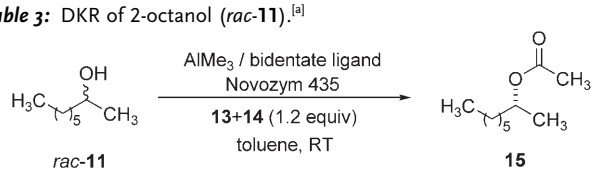
rac-**6** → **10**

Entry	Ligand	$AlMe_3$ [equiv]	*t* [h]	Conv. [%]	Yield of **10** [%]	*ee* [%]
1	(*R*)-binol	0.2	19	98	98	99
2	binol	0.2	19	97	97	99
3[b,c]	2,2′-biphenol	0.2	9	98	98	99
4	2,2′-biphenol	0.2	14	97	97	99

[a] Unless otherwise noted, reactions were run on a 0.625-mmol scale at RT under Ar atmosphere with **8**/**9** (ca. 1:2, 1.2 equiv) as the acylating agent and with 4 mg of Novozym per mmol of alcohol. Yields and *ee* values were determined by chiral GC. The bidentate ligand and $AlMe_3$ were added in a 1:1 ratio. The configuration of the product **10** was assigned by comparison with data in Ref. [4]. [b] Reaction conducted on a 2.5-mmol scale. [c] Reaction conducted at 60 °C.

In the case of 2-octanol (*rac*-**11**), we again observed that the racemization of the alcohol was slower than that of 1-phenylethanol (*rac*-**1**). In addition, the selectivity of Novozym as the lipase was not optimal as evidenced in the KR of *rac*-**11**: Although the initial values obtained in the KR were satisfactory (48 % yield, and 96 % *ee* of the ester **15** after 20 min), the enantioselectivity dropped considerably upon increasing conversion of *rac*-**11**, reaching values as low as 64 % *ee* (63 % conversion) after 18 h. This decrease results from acylation of the "wrong" enantiomer, (*S*)-2-octanol ((*S*)-**11**), once most of (*R*)-2-octanol ((*R*)-**11**) had been consumed. However, when the racemization of the alcohol **11** was accelerated by addition of more of the Al catalyst, satisfactory results were obtained in the DKR of 2-octanol (*rac*-**11**) as well (Table 3). In the presence of 20 mol % of the $AlMe_3$/2,2′-

Table 3: DKR of 2-octanol (*rac*-**11**).[a]



rac-**11** → **15**

Entry	Ligand	$AlMe_3$ [equiv]	*t* [h]	Conv. [%]	Yield of **15** [%]	*ee* [%]
1[b,c]	2,2′-biphenol	0.2	24	95	95	92
2[b–d]	2,2′-biphenol	0.2	6	98	98	90
3	2,2′-biphenol	0.2	18	92	92	86
4	(*R*)-binol	0.2	18	91	91	77
5[e]	binol	0.2	18	93	93	80

[a] Unless otherwise noted, reactions were run on a 0.625-mmol scale at RT under Ar atmosphere with **13**/**14** (ca. 1:9, 1.2 equiv) as the acylating agent and with 2 mg of Novozym per mmol of alcohol. Yields and *ee* values were determined by chiral GC. Bidentate ligand and $AlMe_3$ were added in a 1:1 ratio. The configuration of the product **15** was assigned by conversion of enantiomerically pure (*S*)-2-octanol to the acetate, and GC co-injection. [b] 1.1 equiv of acylating agent (**13**/**14** ca. 1:9). [c] Reaction conducted on a 2.5-mmol scale. [d] Reaction conducted at 60 °C. [e] Reaction conducted with 4 mg of Novozym per mmol of alcohol.

biphenol catalyst and 1.1 equivalents of the acylating agent (**13**/**14**), ester **15** was obtained in up to 95% yield and 92% *ee* on a 2.5-mmol scale at room temperature (Table 3, entry 1). Comparable results but after shorter reaction times were achieved when the reaction temperature was increased to 60°C (Table 3, entry 2). Reactions run on smaller scale were found to afford slightly lower yields and enantiomeric excesses (Table 3, entry 3). In the case of 2-octanol (*rac*-**11**), binol appeared to be less effective than 2,2′-biphenol as a bidentate ligand (Table 3).

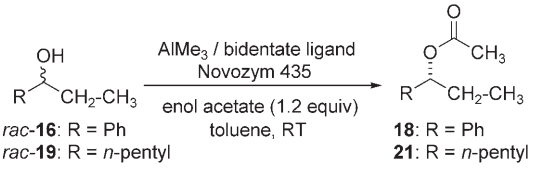
We then extended our study to the DKR of the 1-propanol derivatives 1-phenyl-1-propanol (*rac*-**16**) and 3-octanol (*rac*-**19**). Once again, we used "specific" acylating agents that were synthesized from the corresponding ketones propiophenone (**17**) and 3-octanone (**20**). In these cases, the lipase-catalyzed acylation, though highly enantioselective, was rather slow. However, increasing the amount of lipase resulted in almost quantitative yields and high enantioselectivities after 18 h. The DKR of the substrates *rac*-**16** and *rac*-**19** gave excellent results (up to 99% yield and 98% *ee*) with either binol or 2,2′-biphenol as ligands (Table 4).

We postulate that the bisphenol-type ligands play a dual role in the DKR. First, they increase the activity of the aluminum catalyst by impeding aggregation. Second, the bisphenol aluminum complexes maintain their activity toward racemization of the alcohol in the presence of the lipase. In contrast, $Al(OtBu)_3$, prepared in situ from $AlMe_3$ and *t*BuOH, is a highly active racemization catalyst, but it loses its activity almost completely when combined with the lipase. By the application of bisphenolic ligands, the two processes, racemization effected by the aluminum catalyst and acylation mediated by the lipase, become compatible.

Another remarkable feature of the bisphenol-type ligands is that they increase the activity of the aluminum catalyst towards racemization but not acylation. When $Al(OtBu)_3$ prepared in situ was used as the catalyst for the DKR of 1-phenylethanol (*rac*-**1**), we observed nonenantiospecific chemical esterification at a rate comparable to the racemization of the alcohol. On the other hand, the Al/binol catalyst, although it is a Lewis acid, was shown in control experiments to only weakly promote the direct chemical esterification of 1-phenylethanol (*rac*-**1**). Under these conditions, the substantially higher activity of the lipase towards acylation ensures high product enantiopurity (Table 1). We also deduce from the results obtained in the DKR of the other substrates that such direct "chemical" esterification of the alcohol is not promoted considerably by the Al/2,2′-biphenol catalyst either.

In summary, we have demonstrated that chemoenzymatic DKR of secondary alcohols is possible in high yields and high enantioselectivity through the use of an inexpensive and readily available aluminum catalyst generated in situ in combination with a lipase. We expect that this procedure, owing to the mild conditions and the simplicity of operation, will prove useful for the preparation of a variety of optically pure secondary alcohols, also on larger scale.

Table 4: DKR of *rac*-**16** and rac-**19**.[a]



rac-**16**: R = Ph
rac-**19**: R = *n*-pentyl

18: R = Ph
21: R = *n*-pentyl

Entry	Alcohol	Ligand	$AlMe_3$ [equiv]	Prod.	Yield [%]	*ee* [%]
1	*rac*-16	binol	0.1	(*R*)-**18**	99	98
2	*rac*-16	2,2′-biphenol	0.1	(*R*)-**18**	97	97
3[b]	*rac*-19	binol	0.2	(*R*)-**21**	95	95
4[b]	*rac*-19	2,2′-biphenol	0.2	(*R*)-**21**	95	94

[a] Unless otherwise noted, reactions were run on a 0.5-mmol scale over 18 h at RT under Ar atmosphere with 1.2 equiv of the acylating agents (prepared from propiophenone (**17**) and 3-octanone (**20**), respectively; see the Supporting Information for experimental details) and with 80 mg of Novozym per mmol of alcohol. Yields and *ee* values were determined by chiral GC. Bidentate ligand and $AlMe_3$ were added in a 1:1 ratio. The configuration of the product **18** was assigned by comparison with data in Ref. [4]. The configuration of the product **21** was assigned in analogy to the DKR of 2-octanol (*rac*-**11**). [b] The reaction was conducted with 40 mg of Novozym per mmol of alcohol.

Experimental Section

All reactions were performed under argon atmosphere in oven-dried glassware. Toluene was dried over sodium and distilled under argon atmosphere. All commercially available chemicals were used without further purification. GC analysis was performed using a CP-Chirasil-Dex CB phase column.

DKR of *rac*-**1**: A Schlenk tube was charged with binol (72 mg, 0.25 mmol, 0.1 equiv), 4 mL of a stock solution of trimethylaluminum in absolute toluene (62.5 mM, 0.25 mmol, 0.1 equiv) was added, and the resulting solution was stirred for 15 min at RT. *rac*-**1** (0.302 mL, 305 mg, 2.5 mmol, 1 equiv) was added, and the resulting solution was stirred for a further 5 min. Subsequently, Novozym 435 (30 mg), diphenyl ether (internal standard) (0.397 mL, 2.5 mmol, 1 equiv), and **3** (3 mmol, 1.2 equiv) were added. Argon atmosphere was maintained throughout the reaction. Yields were determined by GC. Samples of 20 μL were withdrawn from the reaction mixture by means of a syringe, diluted to 1 mL with CH_2Cl_2/MeOH (1:1), and filtered through a pad of cotton.

DKR of *rac*-**6** on preparative scale: A 50-mL flask was charged with 2,2′-biphenol (0.29 g, 1.56 mmol, 0.2 equiv), 12.5 mL of a stock solution of trimethylaluminum in toluene (0.125 M, 1.56 mmol, 0.2 equiv) was added, and the resulting solution was stirred for 15 min at RT. *rac*-**6** (1.075 mL, 1.00 g, 7.8 mmol, 1 equiv) was added, and the resulting solution was stirred for a further 5 min. Subsequently, Novozym 435 (31 mg), dodecane (internal standard) (1.774 mL, 7.8 mmol, 1 equiv), and 1.34 mL (7.8 mmol, 1 equiv) of the acylating agent (**8**/**9** ca. 1:2) were added. The resulting mixture was allowed to stir at RT for 24 h. Argon atmosphere was assured throughout the reaction. The solution was filtered through a pad of celite, washed with CH_2Cl_2, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc (95:5). The product ester **10** ($R_f = 0.27$) was obtained as a colorless oil (1.18 g, 90%, 99% *ee*). The ^1H and ^{13}C NMR spectroscopic data obtained from this material were identical to those in the literature.[4]

Supplementary Information contains all experimental details for the synthesis and characterization of the racemic acetates used for the calibrations (*rac*-**5**, *rac*-**10**, *rac*-**15**, *rac*-**18**, and *rac*-**21**), and acylating agents (enol acetates of the ketones **2**, **7**, **12**, **17**, and **20**). Furthermore, the procedures for the DKR of the alcohols (*rac*-**1**, *rac*-**6**, *rac*-**11**, *rac*-

16, and *rac*-**19**), methods used for GC analysis, and retention times of substrates, products, and internal standards are given.

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