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Ruthenium- and lipase-catalyzed DYKAT of 1,2-diols: an enantioselective synthesis of *syn*-1,2-diacetates

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Abstract—Regio- and stereoselective lipase-catalyzed kinetic resolutions were investigated for some unsymmetrical, secondary/secondary *syn*-diols. *Candida antarctica* lipase B-catalyzed transesterifications of a few aryl/alkyl- and alkyl/alkyl 1,2-diols were coupled in one-pot for efficient ruthenium-catalyzed epimerization and intramolecular acyl migration to give a dynamic kinetic asymmetric transformation (DYKAT) affording enantioenriched (ee up to >99%) *syn*-diacetates as the main diastereomers (*syn*:*anti* ~2:1 to 10:1).

1. Introduction

Chiral vicinal diols are important building blocks in enantioselective synthesis. Highly enantioenriched *syn*-1,2-diols are readily available by the Sharpless asymmetric dihydroxylation (AD).[1] Alternative 'greener' protocols for the latter transformation are available, which employ environmentally benign terminal oxidants, such as hydrogen peroxide[2] or molecular oxygen.[3] Another entry to enantioenriched diols is provided by lipase-catalyzed resolution of racemic diols. Amongst the structures containing the 1,2-diol motif, lipases have been extensively used for selective protection and deprotection in carbohydrates and terminal 1,2-diols,[4] regioselective reactions of glycerides,[5] and sequential resolutions of symmetrical diols.[6] However, neither normal nor sequential lipase-catalyzed resolutions of unsymmetrical acyclic *vic*-diols with two stereogenic centers seem to have been much explored. To the best of our knowledge, there are only two reports on the kinetic resolution of 1-phenyl-1,2-propanediol **1a** and neither uses *Candida antarctica* lipase B (CALB). Kim et al. performed the transesterification of *anti*-**1a** using *Pseudomonas cepacia* lipase to obtain at 53% conversion of one major monoacetate and one minor diacetate.[7] More recently, Lee and Ley screened seven lipases (CALB not included) for the regioselective protection of *syn*-**1a** of the alcohol next to the phenyl group.[8]

Kinetic resolutions are limited to a maximum yield of 50% of enantiopure product. In a kinetic asymmetric transformation (KAT) of a diastereomeric 1:1 *syn*:*anti* mixture, the maximum theoretical yield of one enantiomer is 25%. This is a severe drawback, and methods to improve the yield of these reactions are of great importance. We recently reported on different types of dynamic kinetic asymmetric transformations (DYKAT) of symmetrically and unsymmetrically substituted 1,3- and 1,4-diols.[9] In the case of unsymmetrical 1,3-diols, the DYKAT procedure relies on an intramolecular acyl migration in an intermediate monoacetate. An efficient approach toward enantiopure *syn*-1,2-diols would be to combine a lipase-catalyzed transesterification, a ruthenium-catalyzed epimerization, and an intramolecular acyl migration. Unsymmetrical diol **1** would be acylated by the enzyme preferentially at the hydroxyl group closest to the small substituent (Scheme 1). In the presence of a ruthenium catalyst, epimerization should occur and all of **1** would be transformed to **2**, in which one stereocenter is defined. If acyl migration in the *syn*-diol monoacetate of **2** is favored over migration in the corresponding *anti*-diol monoacetate, acetyl migration under dynamic conditions will give only **3**. Subsequently, **3** would be acylated again by the enzyme at the alcohol released to give enantiopure *syn*-diacetate **4**.

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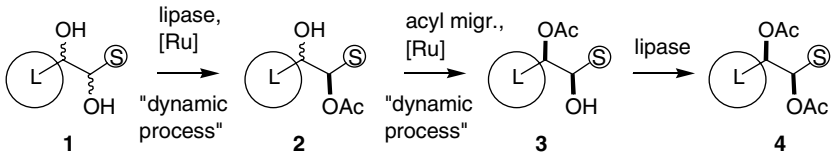


Scheme 1. DYKAT of unsymmetrical acyclic 1,2-diols containing one large substituent (L) and one small substituent (S).

Acyl migration in related 1,2-diols is an often observed phenomenon and has been observed to occur, for example, during hydrolysis of terminal 1,2-diols[10] and in mono- and diglycerides,[11] thus hampering the regioselectivity of lipases.

2. Results and discussion

2.1. Enzymatic transesterification

Enzymatic acylation of *rac-syn*-**1a** using CALB and isopropenyl acetate was studied in toluene at 50 °C (Scheme 2). Surprisingly, not only monoacetate **2a** formed, but also monoacetate **3a** and the two monoacetates **2a** and **3a** in a ca. 3:1 ratio. At higher conversion, small amounts of diacetate **4** were also observed. The formation of **3a** should occur via direct enzymatic acylation of the inner alcohol, since in a controlled experiment it was shown that CALB does not catalyze any significant acyl migration.[12] The selectivity of acylation at the inner alcohol is high and follows Kazlauskas' rule. For example, at 42% conversion (60 min) **3a** was obtained in 11% yield and 96% ee. At this conversion, no diacetate **4a** was formed.

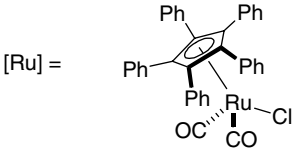
In contrast, the formation of major monoacetate **2a** is less selective. At 13% conversion (24 min), **2a** was obtained in 10% yield and ~86% ee (along with 3% yield of **3a**), which corresponds to $E \sim 14$ (Table 1, entry 1). Kinetic resolutions of a few more diols were investigated. Interestingly, the ratio for **2**:**3** was significantly larger for substrates *rac-syn*-**1b** (Table 1, entry 2), *rac-syn*-**1c** (entry 3), and *rac-syn*-**1d** (entry 4). Acetate **2b** was obtained in 96% ee. Diol *rac-syn*-**1e** (entry 5) behaved the same as **1a**.

A prolonged reaction time was required for consecutive acetylations to diacetate to occur (Scheme 2). The transformation to diacetate is a KAT. After 21 h, 7% of **4a** was produced. Carrying out the reaction in the presence of sodium carbonate (1 equiv) led to a faster production of diacetate.

From a controlled experiment, in which racemic *syn*-monoacetate **3a** was subjected to kinetic resolution, it was concluded that the second acylation is somewhat slower than the first acylation (29% diacetate in 70 min).

2.2. Ruthenium-catalyzed epimerization

Next, epimerization of racemic *syn*-diols **1** was successfully effected by ruthenium complex **5**.[13] This is a precatalyst, which is best activated by *t*-BuOK. We recently reported racemization of secondary alcohols catalyzed by **5**, in combination with lipase-catalyzed kinetic resolution in a very efficient dynamic kinetic resolution (DKR) operating at room temperature.[14] Table 2 shows that under the conditions employed for transesterification of **1a** (50 °C, 0.5 M substrate concentration), epimerization of diols **1a** and **1b** occurs easily (Table 2, entries 1 and 2). Efficient epimerization of diol **1c** required slightly more of catalyst **5** (3 mol %) and a higher temperature (entry 3). In contrast, aliphatic diol **1d** epimerized even at room temperature (entry 4). Epimerization of diols **1e** and **1f** was performed at 50 °C because of their low solubility in toluene at room temperature (entries 5–6). The diastereomeric ratios remained unchanged after prolonged reaction times. The *threo* isomers are the thermodynamically most stable ones. In agreement with our mechanistic investigations of the racemization process,[15] analysis by NMR spectroscopy showed only trace amounts of ketones.



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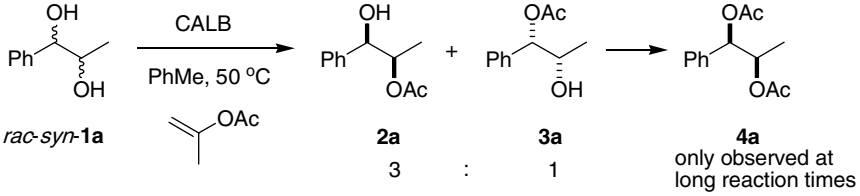
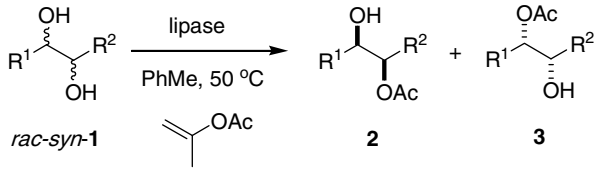
2.3. Intramolecular acyl migration

To obtain information about the rate of acyl migration, this process was studied separately. When *syn*-diol monoacete *rac*-**2a** was heated in deuterated toluene at 50 °C, no acyl migration occurred.[16] Acyl transfer of



Scheme 2. Kinetic asymmetric transformation of *rac*-syn-**1a**.

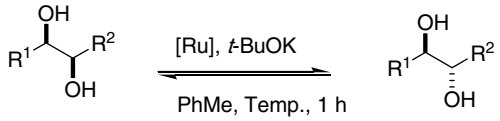
Table 1. Kinetic resolution of *syn*-diols[a]



Entry	Diol	R^1	R^2	Time (min)	Yield[b] (%)		ee (%)[c]		$\sim E$[d]	
					2	**3**	**2**	**3**	**2**	**3**
1	*rac-syn*-**1a**	Ph	Me	24	10	3	86	96[e]	14	n.c.[f]
2	*rac-syn*-**1b**	*n*-Pentyl	Me	7	20	3.8	96	n.d.	61	n.c.[f]
3[g]	*rac-syn*-**1c**	Ph	CO_2Me	210	26	3.4	n.d.	n.d.	n.d.	n.d.
4	*rac-syn*-**1d**	*n*-Butyl	Et	20	10	1[h]	>92[i]	n.d.	>26	n.d.
5	*rac-syn*-**1e**	*p*-OMePh	Me	24	13	3	86	n.d.	15	n.d.

[a] Isopropenyl acetate (3 equiv) was added to a mixture of diol and CALB (20 mg/mmol **1**) in toluene (2 mL/mmol **1**) and the reaction stirred at 50 °C under argon.
[b] Determined by NMR.
[c] ee measured by chiral GC or HPLC after separation by flash column chromatography and chemical acetylation to diacetate.
[d] Since this is a parallel kinetic resolution, the *E* values are not readily calculated from the data. For the larger component, the *E*-value was estimated as if it were an ordinary kinetic resolution.
[e] Measured at 42% conversion.
[f] n.c. = not calculated.
[g] PCL 'Amano' II (80 mg/mmol **1**) was used.
[h] At 20% conversion (30 min) still only 1% **3d** was detected.
[i] Regioisomers **2d** and **3d** are inseparable on silica, hence the ee determination of **2d** is disturbed by the small traces of **3d**.

Table 2. Epimerization of *syn*-**1**[a]

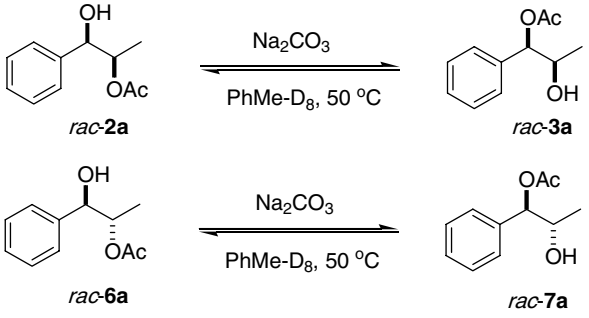


1a R^1 = Ph, R^2 = Me
1b R^1 = *n*-Pentyl, R^2 = Me
1c R^1 = Ph, R^2 = CO_2Me
1d R^1 = *n*-Butyl, R^2 = Et
1e R^1 = *p*-OMePh, R^2 = Me
1f 1,2,3,4-tetrahydro-naphthalene-1,2-diol

Entry	Diol	Temp (°C)	dr (*syn*/*anti*)[b]
1[c]	**1a**	50	2:1
2	**1b**	50	3:2
3[d]	**1c**	80	3:1
4	**1d**	rt	2:1
5	**1e**	50	2:1
6[e]	**1f**	50	5:2[f]

[a] Unless otherwise noted, *t*-BuOK (0.5 M in THF, 2 mol %) was added to a solution of [Ru] (1 mol %) in toluene (1 mL). After 6 min, a solution of diol **1** (1 mmol) in toluene (1 mL) was added and the mixture was stirred and heated at the temperature indicated under an argon atmosphere.
[b] Diastereomeric ratio measured by ^1H NMR.
[c] 2 mol % [Ru] and 4 mol % *t*-BuOK.
[d] 3 mol % [Ru] and 6 mol % *t*-BuOK.
[e] 2 mL of toluene was used because of the poor solubility of diol **1f**.
[f] After 16 h dr = 5:4.

rac-**2a** was, however, observed in a similar experiment run in the presence of 1 equiv of sodium carbonate (Scheme 3); after 4 h, *rac*-**2a**:*rac*-**3a** = 57:43 and this ratio remained constant showing that the acyl migration had reached equilibrium.



Scheme 3. Acyl migration in racemic *syn*- and *anti*-diol monoacetates.

The DYKAT process outlined in Scheme 1 relies on a faster acyl migration in the *syn*-diol monoacetate than in the *anti*-diol monoacetate.[17] The relative rate of acyl migration in *syn*-diol monoacetate **2a** and *anti*-diol monoacetate **6a** was therefore compared. The *anti*-derivative *rac*-**6a** was heated in toluene at 50 °C in the presence of carbonate, as described for *rac*-**2** above. The ratios **3a**/**2a** and **7a**/**6a** from the two experiments, respectively, were calculated and plotted as a function of time (Fig. 1). This study shows that the acyl transfer in *syn*-derivative **2a** is almost three times as fast as in the *anti*-derivative **6a**.

2.4. DYKAT of 1,2-diols

DYKAT of diol **1a** was studied with 5 mol % of **5** and 5 mol % *t*-BuOK and in the presence of Na_2CO_3. After 24 h, all of the diol had been consumed and ~38% diac-

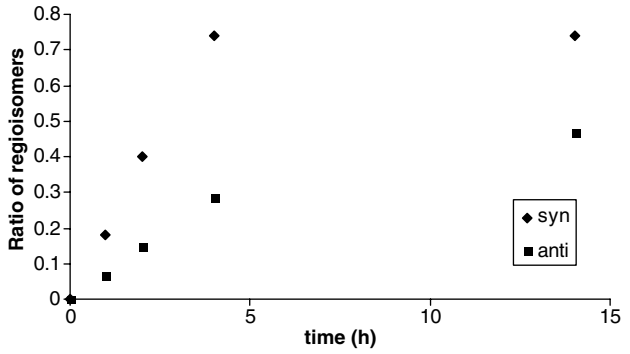


Figure 1. Acyl migration in *syn*- versus *anti*-diol monoacetes. Ratios **3a**:**2a** (*syn*) and **7a**:**6a** (*anti*) are plotted.

etate (of *syn*/*anti* ~2:1) was obtained (Table 3, entry 1). The reaction went to completion after a prolonged reaction time (entry 2). An increased amount of enzyme gave a faster reaction (entries 3 and 4). DYKAT run as in entry 4, but at 70 °C gave a similar result where the ^{1}H NMR spectroscopy indicated a somewhat greater amount of ketones formed (not shown in the table). That the system is sensitive to water is clearly demonstrated in entries 5 and 6 where even more enzyme was used, hence more water in the system, and a slow reaction with lower ee was obtained. The higher dr of **4a** is further evidence that epimerization was inhibited, as the starting material was pure *syn*-diol.

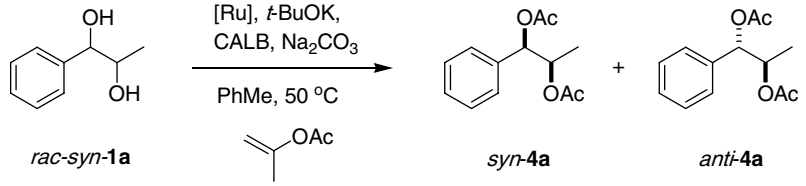
The long reaction time required for the quantitative formation of diacetate in KAT and DYKAT seems to be due to a combination of a slow acyl transfer and a not very fast second acylation. The low dr obtained in DYKAT is ascribed to acyl migration in the *anti*-diol monoacetate (obtained from epimerization of **2a**) and to the formation of the monoacetate at the benzylic position **3a** with an (*S*)-configuration.

A few more diols were exposed to the DYKAT and the results are summarized in Table 4. The required amount of base to activate pre-catalyst **5** depended on the amount of enzyme employed as well as the substrates and hence, had to be optimized for each entry.[14] The acyclic diol **1b** gave a high yield of diacetate **4** as a 2:1 *syn*:*anti* mixture (Table 4, entry 2). Both diastereoisomers were of high ee. Interestingly, diol **1d** mainly gave *syn*-diacetate **4d** (*syn*:*anti* = 10:1) in the DYKAT (entry 3) in high ee. The high diastereoselectivity obtained for this diol in the DYKAT is explained by a more regioselective enzymatic acylation of the alcohol next to the ethyl substituent together with a more *syn*-selective acyl migration in the intermediate monoacetate. Diol **1e** with a *p*-methoxy on the aryl group also worked well in the DYKAT and afforded diacetate **4d** in a 2:1 *syn*:*anti* mixture in high ee (entry 4). The non-optimized result obtained for cyclic 1,2-diol **1f** indicates a lower diastereoselectivity for such substrates (entry 5). Kinetic resolution of *rac*-*syn*-**1f** produced equimolar amounts of regioisomeric monoacetates **2**. The *p*-bromo substituted diol **1g** gave by use of 10 mol % *t*-BuOK only 61% diacetate **4g** after 76 h (entry 6a). The reaction mixture in this experiment turned green, indicating the decomposition of the ruthenium catalyst. When the amount of base was raised to 11 mol %, the reaction mixture remained an orange-color, indicating an active metal catalyst. However, a more chemically acetylated product was obtained (dr = 6:5 and 81% ee, entry 6b).

3. Conclusion

In conclusion, CALB-catalyzed transesterification of **1** has been demonstrated. Regioselective kinetic resolution, in combination with an intramolecular acyl migration and an efficient ruthenium-catalyzed epimerization enantioselectively transforms a mixture of four diol isomers in one-pot to diacetate in moderate to excellent yield and enantioselectivity and in moderate to good diastereoselectivity (~2:1–10:1). The present DYKAT procedure provides a useful alternative to the Sharpless AD reaction since the cost of ruthenium and CALB are not very high.[18]

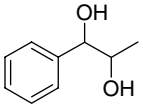
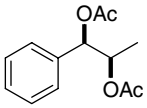
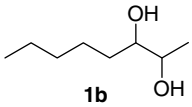
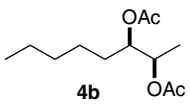
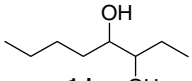
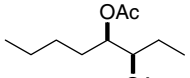
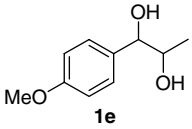
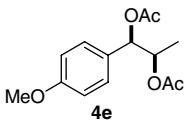
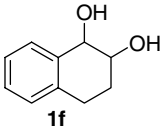
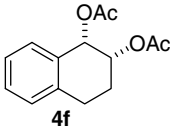
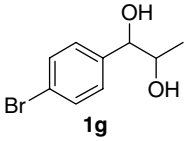
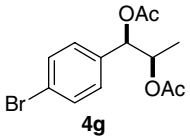
Table 3. DYKAT of 1-phenyl-1,2-propanediol[a]



Entry	Enzyme (mg/mmol)	*t*-BuOK (mol %)	Time (h)	% Conv.[b]	% **4a**[b]	dr[b] (*syn*:*anti*)	% ee[c] (*syn*:*anti*)
1	6	5	24	100	~38	2:1	n.d.
2	6	5	12 d	100	100	2:1	99, >99
3	20	8	24	100	~67	2:1	n.d.
4	20	8	72	100	100	2:1	98, 99
5	60	5	20	100	<50	6:1	n.d.
6	60	5	44	100	~60	3:1	72, n.d.

[a] Ru-catalyst **5** (5 mol %), CALB, Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (1 mL) for 6 min before adding the alcohol (1 mmol) in toluene (1 mL). After 4 min, isopropenyl acetate (3 mmol) was added and the mixture stirred under an argon atmosphere at 50 °C.
[b] Determined by NMR.
[c] Measured by chiral GC.

Table 4. DYKAT of 1,2-diols[a]

Entry	Substrate	Product	*t*-BuOK (mol %)	Time (h)	Yield[b] (%)	dr[c] (*syn*:*anti*)	ee[d] (*syn*, *anti*)
1	 **1a**	 **4a**	8	72	95	2:1	98, 99
2[e]	 **1b**	 **4b**	6	41	95	2:1	96, 99
3a[f]	 **1d**	 **4b**	8	142	87	10:1	>99, >99
3b[g]			9	120	95 (87)	8:1	>99, >99
4	 **1e**	 **4e**	9	72	77 (77)	2:1	98, 99
5	 **1f**	 **4f**	9	65	26 (24)	7:5	>99, ~30
6a	 **1g**	 **4g**	10	76	61 (61)	2:1	90, n.d.
6b			11	73	71 (66)	6:5	81, n.d.

[a] Ru-catalyst **5** (5 mol %), CALB (20 mg), Na_2CO_3 (1 mmol), and *t*-BuOK were stirred in toluene (1 mL) for 6 min before adding the alcohol (1 mmol) in toluene (1 mL). After 4 min, isopropenyl acetate (3 mmol) was added and the mixture stirred under an argon atmosphere at 50 °C.
[b] Determined by NMR or GC. Isolated yield in parenthesis.
[c] Diastereomeric ratio measured by NMR or GC.
[d] Enantiomeric excess determined by chiral GC or HPLC.
[e] CALB: 6 mg.
[f] THF from the *t*-BuOK solution was not evaporated, CALB: 12 mg.
[g] CALB: 12 mg.

4. Experimental

4.1. Reagents and materials

Unless otherwise noted, all reactions were carried out under a dry argon atmosphere in flame-dried glassware. Solvents were purified by standard procedures. Isopropenyl acetate was stirred over K_2CO_3 overnight, dried over $CaCl_2$ and distilled under argon. *C. antarctica* lipase B (CALB) was used as immobilized and thermostable Novozyme 435. *P. cepacia* (PCL) was used as immobilized PS-C Amano II. The enzymes were stored in a sealed container with a saturated aqueous solution of LiCl for a minimum of 24 h. Ruthenium complex **5** was prepared as previously reported.[14b] Diols **1a**–**f** were synthesized by osmium-catalyzed dihydroxylation[19] of commercially available alkenes, and diol **1g** was prepared by Wittig olefination of commercial *p*-bromobenzaldehyde followed by dihydroxylation. ^{1}H NMR data of **1a**,[20] **1b**,[21] **1c**,[22] and **1e**[23] were in agreement with those reported in the literature. Racemic monoacetate **6a** was prepared by epoxidation[24] and subsequent alkaline hydrolysis[25] of *trans*-β-methylstyrene, followed by chemical monoacylation.

Flash chromatography was carried out either on 60 Å (35–70 μm) silica gel or on an automated system. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 300 MHz and at 100 or 75 MHz, respectively. Chemical shifts (δ) are reported in parts per million, using the residual solvent peak in $CDCl_3$ (δ_H 7.26 and δ_C 77.00) as internal standard, while coupling constants (J) are given in hertz. Enantiomeric excess was determined by analytical gas chromatography employing a CP-Chirasil-Dex CB column and temperature programming as indicated below, or by HPLC employing a Daicel Chi-

ralcel OD-H column or a Daicel Chiralpak AS column along with solvents and flow rates as noted, using racemic and diastereomeric mixtures as references.

4.2. Preparation of stereoisomeric mixtures of 1,2-diols: 1-(4-bromophenyl)-propane-1,2-diol 1g

n-BuLi (1.6 M in hexane, 38 mL, 60.5 mmol) was added dropwise to a stirred, white suspension of ethyltriphenylphosphonium bromide (22.5 g, 60.5 mmol) in THF (84 mL) at −5 °C. The mixture turned red upon the addition. After 1 h 40 min at −5 °C, *p*-bromobenzaldehyde (9.33 g, 50.4 mmol) in THF (84 mL) was added via cannula. The cooling bath was removed and the reaction then allowed to reach room temperature. After 25 h, the reaction was quenched by the addition of brine and extracted with toluene. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated. The resulting suspension was diluted in Et_2O and the insoluble material was removed by filtration. Evaporation of the solvent and flash chromatography of the oily residue gave a *cis*/*trans*-mixture of 4-bromo-β-methylstyrene[26] as a colorless oil (7.55 g, 76%).

To a stirred solution of 4-bromo-β-methylstyrene (7.54 g, 38.3 mmol) and 4-methylmorpholine *N*-oxide monohydrate (5.33 g, 38.3 mmol) in acetone/H_2O 3:1 (40 mL), OsO_4 (2.5 wt % solution in 2-methyl-2-propanol, 4.80 mL, 0.38 mmol) was added at room temperature. The weak exotherm was controlled by a water bath. The reaction was stirred under air overnight. Sodium dithionite (2.3 g) and Mg-silicate (4.6 g) were added and the mixture stirred for another 2.5 h before it was filtered through Celite, which was then washed with EtOAc. The filtrate was washed with brine and the water layer was extracted with EtOAc. The organic phase was concentrated under reduced pressure. Flash chromatography of the residue afforded diol **1g** as a highly viscous oil (6.73 g, 76%, *syn*/*anti* = 6:5[27]). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.51 (m, 2H), 7.19–7.21 (m, 2H), 4.65 (app t, $J = 3.7$ Hz, 0.45H), 4.34 (dd, $J = 7.4$, 3.3 Hz, 0.55H), 3.99 (m, 0.45H), 3.80 (m, 0.55H), 2.77 (br d, $J = 3.3$ Hz, 0.55H), 2.50 (br d, $J = 3.6$ Hz, 0.45H), 2.44 (br d, $J = 3.8$ Hz, 0.55H), 1.95 (br d, $J = 4.9$ Hz, 0.45H), 1.05 (2 × d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer (*syn*): δ 140.0, 131.6, 128.5, 121.9, 78.7, 72.0, 18.7; minor isomer (*anti*) δ: 139.2, 131.3, 128.3, 121.6, 76.6, 71.1, 16.9.

4.2.1. *syn*-3,4-Octanediol 1d.[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39–3.47 (m, 1H), 3.30–3.38 (m, 1H), 1.97 (br s, 2H), 1.21–1.67 (m, 8H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.92 (t, $J = 6.9$ Hz, 3H).

4.2.2. *syn*-1,2,3,4-Tetrahydro-1,2-dihydroxynaphthalene 1f.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.47 (m, 1H), 7.21–7.28 (m, 2H), 7.11–7.16 (m, 1H), 4.71 (dd, $J = 5.6$, 4.1 Hz, 1H), 4.03 (m, 1H), 2.93–3.02 (m, 1H), 2.75–2.85 (m, 1H), 2.29 (d, $J = 6.9$ Hz, 1H), 2.25 (d, $J = 5.9$ Hz, 1H), 2.00–2.11 (m, 1H), 1.90–1.98 (m, 1H).

4.3. Kinetic resolution of *syn*-1,2-diols

To a stirred mixture of diol **1a** (152 mg, 1.0 mmol) and CALB (20 mg) in toluene (2 mL) was added isopropenyl acetate (332 μL, 3.0 mmol) and the reaction then heated in an oil bath at 50 °C. After 24 min, the reaction mixture was filtered. The solvents were evaporated under reduced pressure. ^{1}H NMR showed 10% of monoacetate **2a** and 3% of monoacetate **3a**. Regioisomers **2a** and **3a** were separated by flash chromatography. Enantiomeric excess was determined after conversion into diacetates.

To a stirred solution of monoacetate **2a** (17.7 mg, 0.091 mmol), DMAP (cat.), and triethylamine (0.127 mL, 0.91 mmol) in CH_2Cl_2 (0.8 mL), acetic anhydride (43 μL, 0.46 mmol) was added. The reaction was stirred at rt overnight. TLC showed complete conversion and the reaction mixture was treated with MeOH (five drops). The mixture was diluted with CH_2Cl_2 and was washed with 1 M aq HCl. The water phase was extracted with CH_2Cl_2 and the organic phase was washed with saturated aq $NaHCO_3$, water, and brine. After drying over $MgSO_4$ and evaporation of solvent, ^{1}H NMR showed pure diacetate **4a**. Chiral GC: ee = 86%.

4.4. Epimerization of *syn*-1,2-diols

To a Schlenk flask containing Ru complex **5** (6.5 mg, 0.01 mmol) in toluene (1 mL) was added a solution of *t*-BuOK (0.5 M in THF, 40 μL, 0.02 mmol) under an argon atmosphere. After 6 min, a solution of *rac*-*syn*-diol **1b** (146 mg, 1.0 mmol) in toluene (1 mL) was added. The reaction mixture was then heated in an oil bath at 50 °C and samples were collected under a rigorous argon atmosphere and were analyzed by ^{1}H NMR.

4.5. General procedure for DYKAT

A solution of *t*-BuOK (0.5 M in THF, 180 μL, 0.09 mmol) was added to a 10 mL Schlenk flask. THF was carefully removed under reduced pressure and the flask was then filled with argon. Ru-catalyst (32 mg, 0.05 mmol), CALB (12 mg), and Na_2CO_3 (106 mg, 1.0 mmol) were added quickly. The flask was evacuated and filled with argon. Toluene (1 mL) was introduced and the mixture was stirred for 6 min. Then *rac*-*syn*-diol **1d** (146 mg, 1.0 mmol) in toluene (1 mL) was added, and after 4 min isopropenyl acetate (332 μL, 3.0 mmol) was added. After this, the reaction was heated in an oil bath at 50 °C and stirred for 120 h before the mixture was filtered through Celite. The filter cake was washed with EtOAc (25 mL) and the filtrate was concentrated and analyzed by chiral GC (80 °C cte. for 3 min then 3 °C/min to 140 °C): 95% GC-yield, *syn*:*anti* = 8:1, ee (*syn*) >99%, ee (*anti*) >99% [t_{syn}(major) = 12.2 min, t_{syn}(minor) = 11.5 min, t_{anti}(major) = 11.1 min, t_{anti}(minor) = 10.9 min]. Flash chromatography furnished diacetate **4d**[29] as an oil (200 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) *syn*/*anti*-mixture: δ 4.88–4.98 (m, 1H), 4.99–5.06 (m, 1H), 2.08 (d, $J = 2.5$ Hz, 5.3H), 2.04 (d, $J = 2.7$ Hz, 0.7H), 1.21–1.62 (m, 8H), 0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ 170.6,

170.5, 75.1, 73.5, 30.4, 27.3, 23.8, 22.4, 20.9, 20.8, 13.8, 9.6; minor isomer: δ 170.7, 75.5, 73.9, 29.0, 27.6, 22.4, 21.0, 20.9, 13.9, 9.9 (two carbons are missing due to overlapping with the major isomer).

4.6. Characterization of products[30]

References refer to previously reported spectral data of known compounds.

syn/*anti*-1,2-Diacetoxy-1-phenylpropane **4a**:[31] ^{1}H NMR: 95%, *syn*/*anti* $\approx$ 2:1; chiral GC (80 °C cte. for 30 min then 2 °C/min to 160 °C): t_{syn}(major) = 56.5 min, t_{syn}(minor) = 56.3 min, t_{anti}(major) = 55.0 min, t_{anti}(minor) = 55.2 min. The absolute configuration of the pure *syn* diacetate **4a** was established to be (*R*,*R*) from its specific rotation (negative rotation in chloroform).[32] This is in accordance with Kazlauskas' rule.

syn/*anti*-2,3-Diacetoxyoctane **4b**:[33] chiral GC (120 °C cte. for 15 min): 95% yield, *syn*/*anti* = 2:1, t_{syn}(major) = 8.5 min, t_{syn}(minor) = 8.3 min, t_{anti}(major) = 7.6 min, t_{anti}(minor) = 7.8 min.

syn/*anti*-1,2-Diacetoxy-1-(4-methoxy-phenyl)-propane **4e**:[34] ^{1}H NMR: 77% yield, *syn*/*anti* = 2:1; chiral HPLC (Chiralpak AS, *iso*-hexane/2-propanol 96:4, flow rate 0.5 mL/min): t_{syn}(major) = 18.1 min, t_{syn}(minor) = 30.3 min, t_{anti}(major + minor) = 16.5 min; chiral HPLC (Chiralcel OD-H, *iso*-hexane/2-propanol 99.5:0.5, flow rate 0.5 mL/min): t_{anti}(major) = 28.6 min, t_{anti}(minor) = 31.9 min, t_{syn}(major) = 34.3 min, t_{syn}(minor) = 36.0 min.

cis/*trans*-1,2-Diacetoxy-1,2,3,4-tetrahydro-naphthalene **4f**:[35] ^{1}H NMR: 26% yield, *syn*/*anti* = 7:5; chiral GC (80 °C cte. for 30 min then 1.5 °C/min to 170 °C): t_{syn}(major) = 78.9 min, t_{syn}(minor) = 79.5 min, t_{anti}(major) = 78.7 min, t_{anti}(minor) = 78.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) *syn*/*anti*-mixture: δ 6.94–7.32 (m, 4H), 6.18 (d, J = 3.6 Hz, 0.58H), 6.07 (d, J = 5.9 Hz, 0.42H), 5.15–5.29 (m, 1H), 2.82–3.12 (m, 2H), 1.92–2.35 (m, 6H), 2.11 (s, 1.26H), 2.10 (s, 1.74H), 2.05 (s, 1.74H), 2.04 (s, 1.26H); ^{13}C NMR (75 MHz, $CDCl_3$) *syn*/*anti*-mixture: δ 170.5, 170.4, 170.3, 136.6, 136.6, 132.7, 132.1, 130.0, 129.0, 128.7, 128.7, 128.5, 128.2, 126.5, 126.4, 71.4, 71.0, 70.1, 69.3, 27.1, 25.7, 24.9, 23.3, 21.1, 21.1, 21.0 (two carbons are missing due to overlapping).

syn/*anti*-1,2-Diacetoxy-1-(4-bromo-phenyl)-propane **4g**: ^{1}H NMR: 61% yield, *syn*/*anti* = 2:1; chiral HPLC (Chiralcel OD-H, *iso*-hexane/2-propanol 98:2, flow rate 0.5 mL/min): t_{syn}(major) = 15.5 min, t_{syn}(minor) = 19.1 min, t_{anti}(major + minor) = 13.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) *syn*/*anti*-mixture: δ 7.18–7.26 (m, 2H), 7.46–7.53 (m, 2H), 5.83 (d, J = 4.4 Hz, 0.35H), 5.70 (d, J = 7.1 Hz, 0.65H), 5.14–5.27 (m, 1H), 2.13 (s, 1.05H), 2.08 (s, 1.95H), 2.02 (s, 1.95H), 2.00 (s, 1.05H), 1.17 (d, J = 6.6 Hz, 1.05H), 1.09 (d, J = 6.6 Hz, 1.95H); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer (*syn*): δ 170.1, 169.8, 135.9, 131.7, 129.0, 122.6, 76.6, 71.0, 21.0, 20.9, 16.4; minor isomer (*anti*) δ: 170.1, 169.7, 135.6, 131.5, 128.7, 122.2, 75.5, 71.2, 21.0, 21.0, 14.8.

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