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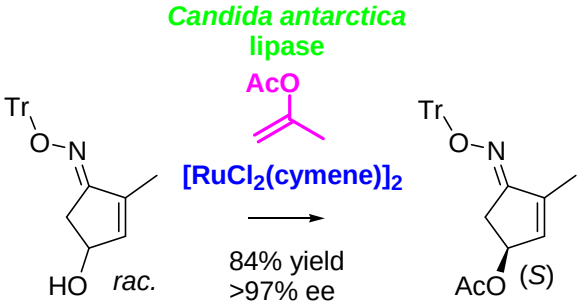

Studies towards dynamic kinetic resolution of 4-hydroxy-2-methylcyclopent-2-en-1-one and its *E*-*O*-trityl oxime

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Abstract:

Dynamic kinetic resolution through metal complex induced racemization and *Candida antarctica* lipase mediated enantioselective acetylation of a model hydroxy-ketone: 4-hydroxy-2-methylcyclopent-2-en-1-one and its selected derivatives, has been studied. Racemization of the hydroxy-ketone was efficiently affected by $[RuCl_2(cymene)]_2$ complex - triethylamine while Shvo's catalyst triggered an intramolecular redox process. Kinetic resolution of 4-hydroxy-2-methylcyclopent-2-en-1-one with *C. antarctica* under conditions compatible with $[RuCl_2(cymene)]_2$ racemization failed to reach the efficiency threshold. However, dynamic kinetic resolution of its *O*-trityl oxime using $[RuCl_2(cymene)]_2$ –

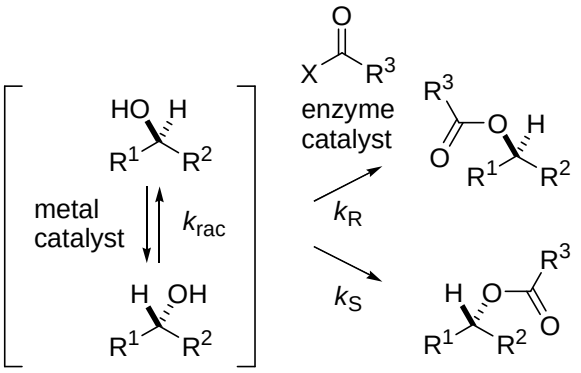
triethylamine and *C. antarctica* lipase – isopropenyl acetate combination, was successfully achieved.

Keywords: dynamic kinetic resolution, ruthenium chloride cymene dimer, Shvo's catalyst, 3-hydroxyl-cyclopent-2-en-1-one

Introduction

Dynamic kinetic resolution (DKR) of racemic secondary alcohols, pioneered by Williams[1] and Bäckvall,[2] provides an important connection between racemic and optically active compounds.[3,4] An advanced version of DKR utilizes a lipase as an enantio-differentiating factor, an acylating agent and metal racemization catalyst. The principles of this method are illustrated in Scheme 1. The alcohol enantiomers react with chiral acylating agent – enzyme assembly at different rates, k_R and k_S generating a non-racemic mixture of the acyl derivatives and residual alcohols (kinetic resolution, KR). Simultaneously, the metal racemization catalyst brings about equilibrium between (*R*)- and (*S*)-alcohols thus providing the continuous replenishment of the alcohol enantiomer that is acylated at the higher rate. The process continues until all available racemate is transformed into the enantiomerically enriched ester. Ideally, in a case of a large difference between k_R and k_S, ester of the faster reacting alcohol would be obtained in a nearly optically pure form and a quantitative yield. For effective DKR it is important[3c] that the difference in the reaction rates of enantiomers would be relatively large (practically, $E = k_R/k_S$ larger than 20 is required for $k_R > k_s$) and that the ratio between racemization rate (k_{rac}) and the slower acylation reaction rate (k_S) would be significant (larger than 10).

Scheme 1. General features of dynamic kinetic resolution (DKR).



Several catalysts effecting racemization of secondary alcohols are known,[5,6] however only a few of them have been successfully applied in combination with an acyl donor and an enzyme preparation. Thermally activated di-ruthenium complex **1** (Fig. 1, Shvo's catalyst[5a]) has been first employed for DKR of racemic secondary alcohols in combination with *Candida antarctica* lipase[7] B (CALB, Novozyme 435®) and *p*-chlorophenyl acetate as the acetyl donor.[2] The Kim - Park catalyst[5b,5c] **2** (activated with *tert*-BuOK) has been developed for application in combination with CALB and isopropenyl acetate (IPA). Bäckvall's catalyst[5d,5e] **3** (activated with *tert*-BuOK) was found to function well in combination with CALB and IPA. Ruthenium cymene dimer **4** activated by triethylamine has been used with a lipase *Pseudomonas cepacia* (PCL) and *p*-chlorophenyl acetate for DKR of allylic alcohols.[8] The same ruthenium complex **4** – in combination with tertiary amine, *p*-chlorophenyl acetate and CALB has been applied more recently by the Deca workers[9] for DKR of various benzylic alcohols. These authors have observed that the racemization rate depends significantly upon the nature of amine used for activation of catalyst and they found that the combination of **4** and *N,N,N',N'*-tetramethylpropanediamine provides the best system. Catalysts based upon ruthenium complex **4** appear to be of particular interest because of its stability towards atmospheric oxygen and moisture, and availability at relatively low price.

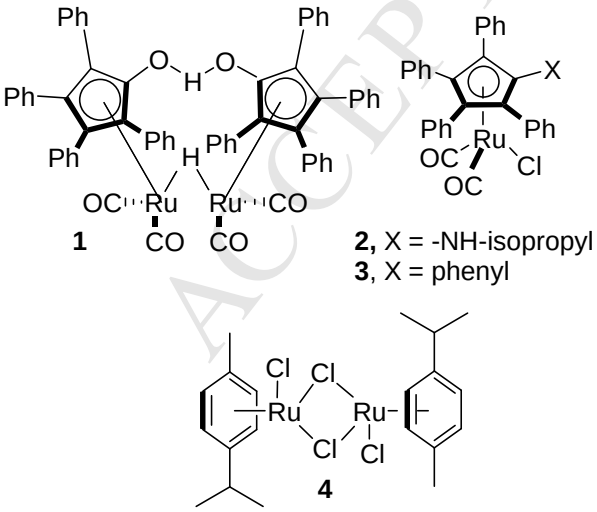
DKR with ruthenium catalysts have been applied to a variety of "functionalized" secondary alcohols.[3a,3c] However, there are available only a few reports concerning the racemization of

hydroxy-ketones,[10] in which a competing process - an intramolecular hydride transfer, could take place.

It was of interest to examine racemization and eventually DKR of the hydroxy ketone, 4-hydroxy-2-methylcyclopent-2-en-1-one **5** (Scheme 2), which constitutes a convenient starting material for the terpenoid synthesis.[11,12] Recently, we have developed a preparative procedure for kinetic resolution of *rac*-**5** using CALB and IPA.[13,14] However, the attained efficiency (*E* = ca. 15 in *tert*-butyl methyl ether) did not reach the threshold required for the effective DKR. As an alternative, preparation of derivatives of **5** with anticipated higher *E* values in the kinetic resolution and their application in KR in DKR was considered.

In this paper we report the initial studies on racemization of hydroxy-ketone **5** using catalysts **1** and **4**, and the preparation, configurational assignments and kinetic resolution of *E*-*O*-trityloxime *E*-**9**. The latter derivative, *rac*-*E*-**9,** has been successfully used in the dynamic kinetic resolution process using catalyst **4**, triethylamine, CALB and IPA.

Figure 1. Selected catalysts for the racemization of secondary alcohols.

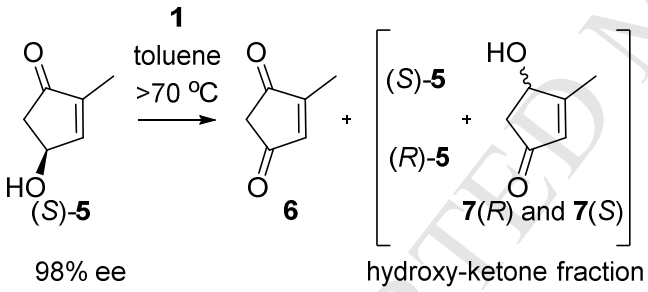


Results and Discussion

*Racemization of hydroxy-ketone **5**.*

Heating (*S*)-**5** (98% *ee*) and the catalyst **1** (2 mol%) in toluene at 70 ºC for 24 h followed by separation of the products by chromatography afforded dione[15] **6** and a hydroxy-ketones fraction in 23% and 74% yields, respectively (Scheme 2). HPLC analysis (chiral column) and inspection of the ^{1}H NMR spectra of the hydroxy-ketone fraction showed it to consist of (*S*)-**5** (49%), (*R*)-**5** (4%) and two other components to which the structures of (*R*)- and (*S*)-**7** were assigned (25% and 22%).[16] An analogous reaction of (*S*)-**5** and **1** at 100 ºC afforded **6** (51%) and the hydroxy-ketone fraction, 13%, containing (*S*)-**5** and (*R*)-**5** in almost equal amounts (22% and 21%) as well as the enantiomers of **7** (29 and 27%).

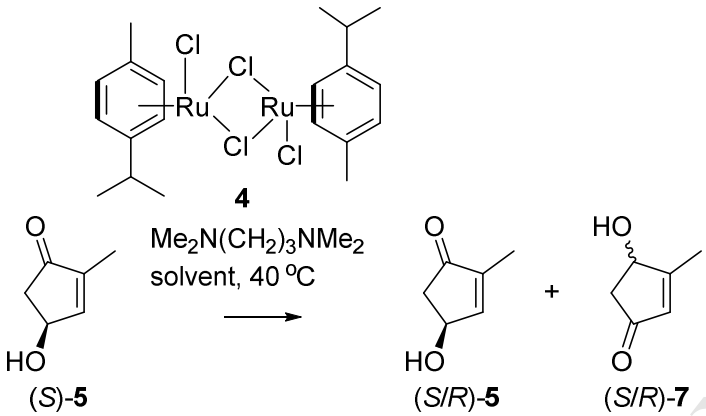
Scheme 2. Racemization of (*S*)-**5** using Shvos's catalyst **1**.



In further experiments we examined cymene ruthenium complex **4** (2 mol%) - *N,N,N',N'*-tetramethylpropanediamine (90 mol%).[9] MTBE, toluene, chlorobenzene and 1,2-dichloroethane (DCE) were chosen as the solvents and the reactions were carried out at 40 ºC. As shown in Table 1, in all of the solvents after 20 h the hydroxy-ketone recovery was high with only small amounts of the "reversed" isomer **7** formed as a side product. The degree of racemization expressed as the racemization capacity[9] ($\Delta ee = ee_0 - ee_t$) depended on the nature of solvent. The best results were obtained in DCE with Δee amounting to 98% after 20 h (entries 7 and 8). Addition of acetone (3 mol equiv) did not affect the reaction outcome (entry 9). Addition of acetic acid (3 mol equiv) inhibited the racemization (entry 10), which apparently

reflects protonation of the amine. The ^{1}H NMR spectra of the crude products showed the presence of only trace contamination, presumably saturated products.

Table 1. Racemization of (*S*)-**5** (98% *ee*) using cymene ruthenium complex **4**, $[cymRuCl_2]_2$, 2 mol%, and *N*,*N*,*N'*,*N'*-tetramethylpropanediamine[9] (90 mol%) in selected solvents at 40 ºC.



	Solvent[a]	T (h)	Recov. %[b]	(*ee*%)	Δ*ee*[c] (%)	**7%**[d]
1	MTBE	3	-	88	10	-
2		20	88	54.	44	1
3	Tol	3	-	48	50	1
4		20	91	5	93	5
5	ClPh	3	-	43	55	1
6		20	87	3	95	5
7	DCE	3	-	29	69	1
8		20	88	0	98	6
9	DCE[e]	20	-	0	98	6
10	DCE[f]	20	-	98	0	-

[a]Abbreviations: MTBE – tert-butyl methyl ether, Tol – toluene, ClPh – chlorobenzene, DCE – 1,2-dichloroethane.
[b]The product was isolated and purified by chromatography after 20 h; intermediate measurements were carried out on samples taken from the reaction mixture.
[c]Racemization capacity,[9] $\Delta ee = ee_0 - ee_t$.
[d]Content in the mixture, HPLC signal of one enantiomer of **7** partly overlapped with that of (R)-**5**.
[e]Added acetone, 3 mol equiv.
[f]Added acetic acid, 3 mol equiv.

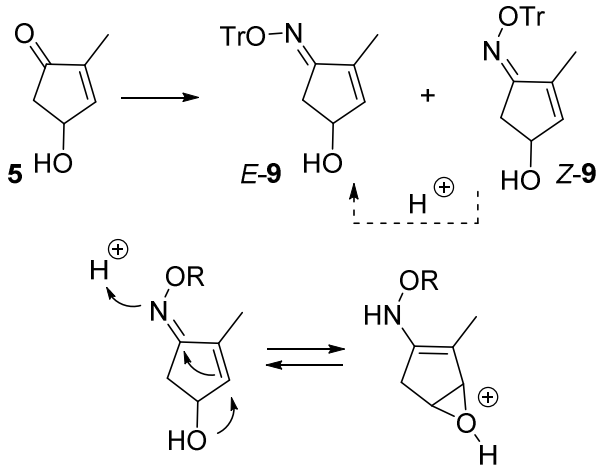
The discussed results show that Ru-cymene **4** catalyst is well suited for racemization of the hydroxy-ketone (*S*)-**5**. Our further experiments on applying DKR to *rac*-**5** turned out to be disappointing because of the *E*-values in the kinetic resolution in the solvents compatible with

the racemization catalyst were too low. It was then decided to search for hydroxy-ketone **5** derivatives that could meet the required criteria for both processes, the CALB-mediated kinetic resolution and the racemization. *O*-Alkyl/aryl oximes have been chosen. Several oximes were prepared from **5** and the corresponding hydroxyamine derivatives.[17] After series of preliminary tests trityloxime **9** (Scheme 3) was selected for further studies.

O-Tritylhydroxyamine **8** that was needed for the preparation of **9** (not previously reported, to the best of our knowledge) was obtained by treating an excess of *N*-hydroxyphtalimide with trityl chloride and triethylamine to form *N*-trityloxyphtalimide followed by hydrazinolysis. Reaction of *rac*-**5** with trityloxyamine **8** followed by flash chromatography on a silica gel column afforded two isomeric products identified as *E*-*rac*-**9** and *Z*-*rac*-**9** (81% and 17% yield, respectively).

Rather unexpectedly, *Z*-**9** smoothly isomerized into *E*-**9** on contact with a trace of acid. On the other hand, a sample of *Z*-**9** was stable on storing and was recovered unchanged after being heated in toluene at reflux temperature for a few hours (with no acid present). The acid-induced isomerization can be explained by the hydroxy group participation in weakening of the carbon-nitrogen double bond and thus lowering the *Z*-*E* rotation barrier, as illustrated in Scheme 3. The relevant intramolecular Michael-type hydroxy group participacion has been postulated to explain some properties of the parent hydroxy-ketone.[18] The corresponding optically active oximes (*S*)-*E*- and (*S*)-*Z*-**9** were prepared starting from (*S*)-**5** (98% *ee*).

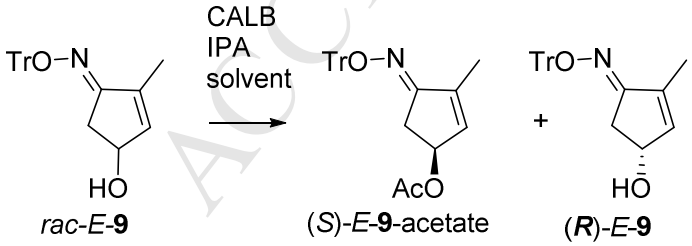
Scheme 3. Preparation of oximes **9**.



*Kinetic resolution of rac-E-**9***

The resolution of *rac-E*-**9** in solvents suitable for the racemization experiments with catalyst **4**: toluene, chlorobenzene and dichloroethane at 40 ºC were examined. As shown in Table 2, resolution of *rac-E*-**9** in DCE was the most efficient with *E* value of ca. 158. It is noteworthy that in the resolution of hydroxy oximes *rac-E*-**9** the (*S*)-epimer is being acetylated at a higher rate, in contrast to the preference observed in resolution of *rac*-**5**. Several cases of similar kinetic preference reversal as the result of substrate modification have been reported.[19]

Table 2. Kinetic resolution of *rac-E*-**9** using CALB (10% w/w) and IPA (3 mol equiv) at 40 ºC in selected solvents (3% solution).



	Solvent[a]	T (h)	Conv. (%)	(*S*)-OAc *ee*%	(*R*)-OH *ee*%	E[b]
	Tol	2 20	10 51	87 74	9 80	16
	ClPh	2 20 44	6 40 53	92 86 79	6 44 88	23

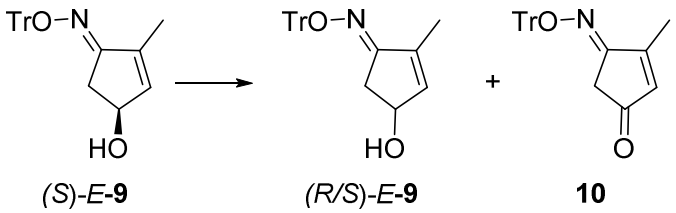
	DCE	2 20 44 72 5d	.4 24 38 44 50	98 98 98 97 96	4 30 58 76 95	158

[a]Solvent name abbreviations are as in Table 1.
[b]E values were calculated accordingly to the literature protocol.[20]

*Racemization of E-**9** in DCE*

In preliminary experiments to assess the affect of catalyst **4** and a tertiary amine on (*S*)-*E*-**9** and some other hydroxy *O*-alkyl oximes, no products of the carbon – nitrogen double bond reduction could be detected. Racemization of (*S*)-*E*-**9** (98% *ee*) was examined in DCE at 40 °C using **4** (2 mol%) - *N,N,N',N'*-tetramethylpropylidenediamine (0.8 equiv; Scheme 4). The results are presented in Table 3. As evident, the racemization of (*S*)-*E*-**9** occurred rapidly at the beginning and then the reaction proceeded with a decreasing rate. However, the catalyst activity was sustained throughout the time of measurements. The side product formed during the process was isolated and identified as the oxo-derivative **10**. After 24 h racemization excess (Δ*ee*) amounted to 93% and ketone **10** content to 5%. Addition of acetone (3 mol equiv) accelerated the racemization rate with a slight increase of ketone **10** formation. Supplementary experiments were also carried out using toluene and chlorobenzene as solvents. As it is indicated in Table 3, the racemization rate in toluene was slower than in DCE with a similar rate of ketone **10** formation. Reaction in chlorobenzene gave similar results to those in DCE.

Scheme 4. Racemization of (*S*)-*E*-**9** using catalysts **4** and a base.



*(S)-E-**9*** *(R/S)-E-**9*** **10**

Table 3. Racemization of (*S*)-*E*-**9** using **4** (2 mol%) and *N*,*N*,*N'*,*N'*-tetramethylpropylidenediamine, 0.8 equiv. in DCE at 40 °C.

Solvent[a]	Time	(*S*)-OH, *ee*%	Δ*ee*[b]	Ketone **10**, **%**
DCE	5 min	37	61	3
	15 min	25	73	3
	30 min	23	75	3
	1 h	18	80	4
	2 h	14	84	4
	3 h	14	84	5
	24 h	5	93	5
DCE acetone 3 eq	5 min	22	76	4
	15 min	7	91	7
	30 min	4	93	8
	1 h	2	96	9
	2 h	1	97	10
Tol	3 h	27	71	4
	24 h	14	84	8
PhCl	3 h	11	86	3
	24 h	7	91	8

[a]Solvent name abbreviations are as in Table 1.
[b]Racemization capacity,[9] $\Delta ee = ee_0 - ee_t$.

The *N*,*N*,*N'*,*N'*-tetramethylpropylidenediamine worked well as a base in the racemization experiments, however, an operational disadvantage of using that amine was the formation of viscous mixtures. It was of interest to compare action of *N*,*N*,*N'*,*N'*-tetramethylpropylidenediamine to recommended earlier[8] triethylamine with respect to (*S*)-*E*-**9** racemization. The results are compiled in Table 4. As evident, applying triethylamine results in only slightly lower racemization rate than *N*,*N*,*N'*,*N'*-tetramethylpropylidenediamine. It was decided to use triethylamine in combination with **4** in further experiments.

Table 4. Racemization of (*S*)-*E*-**9** (98 % *ee*) using **4** and *N*,*N*,*N'*,*N'*-tetramethylpropylidenediamine (0.8 mol equiv) or triethylamine (0.8 mol equiv) (DCE, 40 °C).

Time	Propylidenediamine[a]			Et_3N		
	ee%	Δ*ee*	**10**(%)	*ee*%	Δ*ee*	**10**(%)

5 min	37	61	3	39	60	3
15 min	25	73	3	33	65	3
30 min	23	75	3	30	68	4
1 h	20	78	4	26	72	5
2 h	16	82	4	23	75	5
3 h	12	86	4	22	76	6
22 h	7	91	7	18	80	10

[a] *N,N,N',N'*-tetramethylpropylidenediamine.

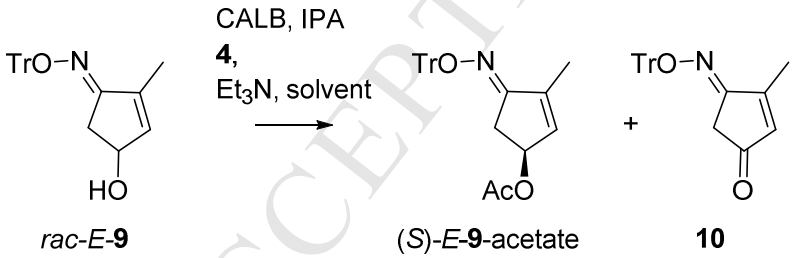
*Dynamic Kinetic Resolution of rac-E-***9**

With the encouraging results for both the kinetic resolution and the racemization of (*S*)-*E*-**9** carried out separately, we approached the dynamic kinetic resolution. In the first series of experiments all components of the reaction mixture, the substrate, CALB, IPA, ruthenium catalyst and triethylamine, were combined at the beginning of the procedure (one-stage transformation). In complementary experiments *rac*-**9**, CALB and IPA were combined and kinetic resolution was allowed to proceed until ca. 40% of conversion was reached. Only then catalyst **4** and triethylamine were added. Typical results are shown in Table 5.

Stirring together a mixture of *rac-E*-**9**, CALB (10 mol%), IPA (3 mol equiv), **4** (2 mol%) and triethylamine (0.8 mol equiv) for 3 days afforded the mixture consisting of acetates (61%) in which (*S*)-enantiomer predominated (>98% *ee*), residual alcohols (32%, *R/S* ratio 2/1) and ketone **10** (7%; Table 5, entry 1). The extension of reaction time to 6 days caused the conversion increase to 75% [(*S*)-*E*-**9**, >98 % *ee*] and the increase of content of ketone **10** to 8% (entry 2). After 10 days the conversion reached 82% [(*S*)-*E*-**9**-acetate, 98% *ee*] and ketone **10**, 10% (entry 3). Carrying the reaction at 60 ºC for 3 days resulted in 66% conversion to acetate (97% *ee*) with increase in the amount of ketone **10** to 23% (entry 4). An increase of amount of CALB to 20% w/w (entry 5) as compared to 10% (entry 1) resulted in an increase of conversion to 76% (97% *ee*) with some decrease in amount of **10** (5%). An extension of the reaction time (entry 6) allowed reaching 88% of conversion (98% *ee*) with a low **10** content, 6%.

When *rac*-*E*-**9** was allowed to react with CALB (10% w/w) and IPA for 2 days (*R*)/(*S*)-*E*-**9**-acetates content was 37.1 and 0.34% by HPLC (entry 7). At this point catalyst **4** and triethylamine were added and the mixture was stirred for additional 5 days. After that time (7 days in total) the conversion reached 85% with optical purity of (*S*)-*E*-**9**-acetate >98% *ee*, and 8% of ketone **10**. Similar results were obtained in 3 and 7 days process (10 days in total, entry 8). When compared to the one-stage process (10 days, entry 3) a higher conversion with a lower content of ketone **10** were recorded. When 20% of CALB was applied and reaction was carried out in 1 and then 5 days (6 days, entry 9) essentially the same results as in "one stage process" (entry 6) were obtained. The two-stage process 1 and 3 days (4 days in total, entry 10) at 60 ºC with 20% w/w of CALB gave 84% of acetate of somewhat lower value of *ee* (95% *ee*) and 11% of ketone **10**.

Table 5. DKR of *rac*-*E*-**9** using CALB, IPA (3 mol equiv), catalyst **4** (2 mol%) and triethylamine (0.8 mol equiv) in DCE.[a]



rac-*E*-**9** (*S*)-*E*-**9**-acetate **10**

	1st Stage		2nd Stage		Total time (days)	CALB (%w/w)	(*S*)-*E*-**9**-acetate,[b] %, (*ee*%)	Alcohols(%) (*R*/*S* ratio)[c]	Ketone **10** (%)
	Temp. (ºC)	Time (days)	Temp. (ºC)	Time (days)					
1	40	3	-	-	3	10	61 (>98)	32 (2/1)	7
2	40	6	-	-	6	10	75 (>98)	17 (2/1)	8
3	40	10	-	-	10	10	82 (>98)	8 (2/1)	10
4	60	3	-	-	3	10	66 (97)	11 (1/1)	23
5	40	3	-	-	3	20	76 (97)	18 (5/1)	5
6	40	6	-	-	6	20	88 (97)	7 (5/1)	6
7	40	2[d]	40	5	7	10	85 (>98)	8 (5/3)	8
8	40	3[e]	40	7	10	10	85 (97)	7 (5/2)	8
9	40	1[f]	40	5	6	20	88 (98)	6 (4/1)	7

10	60	1[g]	60	3	4	20	84 (95)	5 (2/1)	11

[a]The experiments were conducted in ca. 0.15 mmol scale [ca. 50 mg of (S)-E-**9]**, in DCE solution (5%) with magnetic steering, using CALB (as indicated), IPA (3 mol equiv), catalyst **4** (2 mol%) and triethylamine (0.8 mol equiv).
[b]Average of at least 3 measurements.
[c]The less mobile alcohol enantiomer partly overlapped with the ketone on HPLC analysis.
[d]Content of **9**-acetates (S/R) as 37.1/0.3%.
[e]Content of **9**-acetates (S/R) as 44.8/0.6%.
[f]Content of **9**-acetates (S/R) as 35.6/0.3%.
[g]Content of **9**-acetates (S/R) as 47.1/1.3%.

A larger scale experiment was conducted under conditions analogous to those indicated in Table 5, entry 7. Thus, starting from *rac*-*E*-**9** (ca. 300 mg) and using CALB, (10% w/w), IPA (3 mol equiv), ruthenium catalyst **4** (2 mol%) and triethylamine (0.8 mol equiv) in DCE with the reaction time 7 days (*S*)-*E*-**9**-acetate was obtained, 84% yield and 97% *ee*.

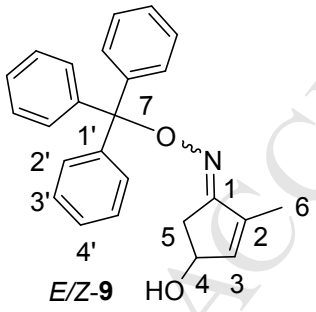
Structure of trityloxime **9**

The calculated energy difference between *Z*- and *E*-**9** oxime isomers amounted to 3 kcal/mol, which led to the presumption that the isolated major product has *E*-configuration. The confirmation of structural assignments of isomers was gained from their ^{13}C NMR spectra in combination with extensive DFT calculations of NMR parameters. The experimental and DFT calculated chemical shifts (δ) of *Z*-**9** and *E*-**9** carbon nucleus are presented in Table 6.

As shown in Table 6, in *Z*-**9**, C2 (proximal to the oxime *O*-atom) resonance appeared at δ 138.10 ppm whereas for *E*-**9** at 140.72 (Δδ = -2.64); the corresponding values for C-5 are 37.68 (*E*-**9**, proximal to the oxime *O*-atom) and 40.28 (Δδ = -2.60). By the nominal value these differences are in agreement with the structure assignment criteria. In the fundamental studies[21] on ^{13}C NMR assignment of oxime isomers structure it was determined that the chemical shift of the carbon α in the position proximal to the oxime OH group appears systematically at higher field with the magnitude of the effect varying (up to 10 ppm). Those observations are in line with the data extracted from works on *O*-alkyl unsymmetrical oxime

isomers[22] and with a recent systematic examination of *O*-alkyl acetone oximes.[23] However, some other features of the ^{13}C spectra of *Z*- and *E*-**9** had no literature precedent and indicated that shielding effects of the oxygen atom *vs.* the nitrogen atom electron pair may overlap with shielding effects arising from other parts of the molecule. In particular, (1) chemical shifts of C1 for *Z*- and *E*-**9**, δ 159.22 and 164.23 ppm, respectively, differ with $\Delta\delta = \delta^{Z}-\delta^{E} = -5.01$ ppm, clearly exceeding the literature values (fitting into the range -0.7 to +0.6 ppm), (2) chemical shifts of the C6 nuclei for *Z*-**9** and *E*-**9** appeared at δ 18.13 and 12.30 ppm, $\Delta\delta = 5.83$, with the opposite sign of the shift than that observed for C2.

Combination of experimental NMR data and DFT calculations of parameters reflecting the shielding effects magnitude and direction fully confirmed the structure assignments. Calculated shielding effects for *Z*- and *E*-**9** are shown in Table 6. The complete ^{1}H, ^{13}C NMR experimental data, calculation details and some comments are presented in the Supporting Information. It should be noted that the propeller-type chirality is inherent to the trityl group.[24] The calculated energy barrier between *M* and *P* diasteroisomers of *Z*- or *E*-(*S*)-**9** do not exceed 0.1 kcal/mol. The measured spectra apparently represent the averaged values of chemical shifts originating from both diastereomers.



E/Z-**9**

Table 6. Experimental and DFT calculated ^{13}C chemical shifts of oximes **9** in benzene and corresponding differences $\Delta\delta^{Z}_{E}$ ($\delta^{Z9}-\delta^{E9}$).

δ^{13}C /ppm						
#	experimental			calculated		
	Z-**9**	*E*-**9**	**$\Delta\delta^{Z}_{E}$**	*Z*-**9**	*E*-**9**	**$\Delta\delta^{Z}_{E}$**
1	159.22	164.23	**-5.01**	167.51	169.82	**-2.31**

2	138.10	140.72	**-2.62**	146.17	146.06	**0.11**
3	146.36	142.40	**3.96**	148.03	145.83	**2.20**
4	70.93	72.83	**-1.90**	70.47	72.54	**-2.07**
5	40.28	37.68	**2.60**	39.36	37.37	**1.99**
6	18.13	12.30	**5.83**	15.41	7.97	**7.44**
7	91.77	91.67	**0.10**	91.56	90.95	**0.61**
1′	145.52	146.12	**-0.60**	148.51	148.14	**0.37**
2′	127.87	128.47	**-0.60**	131.16	130.95	**0.21**
3′	129.87	130.42	**-0.55**	127.86	127.9	**-0.04**
4′	127.34	127.99	**-0.65**	126.85	127.27	**-0.42**

Conclusions

In conclusion, hydroxy ketone *rac*-**5** was transformed into *O*-trityl oxime *rac*-*E*-**9**, which was shown to be a good candidate for kinetic resolution using CALB and IPA. Racemization of (*S*)-*E*-**9** was executed using easily accessible ruthenium catalyst **4** activated with *N,N,N',N'*-tetramethylpropanediamine or with triethylamine in dichloroethane. The oxo-derivative **10** was identified as the only racemization side product (less than 10% yield). DKR of *rac*-*E*-**9** was accomplished using catalyst **4** and triethylamine in combination with CALB and IPA affording (*S*)-*E*-**9**-acetate in 84% yield and 97% *ee*.

A preliminary study on hydroxy ketone (*S*)-**5** racemization showed that Shvo's catalyst **1** (toluene, 70 ºC or higher temperatures) affords mixtures of dione **6** and "reversed" hydroxy ketone **7**. However, catalyst **4** - *N,N,N',N'*-tetramethylpropanediamine (dichloroethane, room temperature) gives appreciable racemization results.

Trityloxyamine **8** was prepared and its reaction with **5** leading to *E*- and *Z*-**9** was investigated.

Experimental

General Experimental Methods.

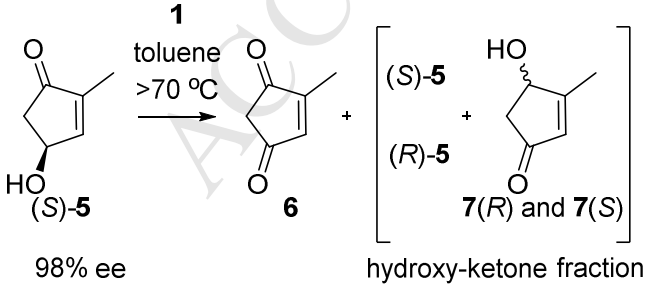
Melting points were determined on a hot-stage apparatus. Optical rotations were measured for $CHCl_3$ solutions on a polarimeter using 1 mL capacity cell (10 cm path length). IR spectra were recorded on FT/IR apparatus. NMR spectra were recorded in $CDCl_3$ or C_6D_6 solutions

on a spectrometers: for ^{1}H at 500 MHz/^{13}C at 125 MHz or 400 for ^{1}H at 400 MHz/^{13}C at 100 MHz. Chemical shifts are quoted on the δ scale taking the solvent signal as the internal standard ($CHCl_3$, ^{1}H, 7.26 ppm; $CDCl_3$, ^{13}C, 77.00 ppm, benzene, ^{1}H, 7.16 ppm, ^{13}C 128.06 ppm). Column chromatography was performed on Merck silica gel 60, 230-400 mesh and TLC - on aluminum sheets, Merck 60F 254. HPLC analyses were conducted using a chiral Daicel Chiralcel AD-H® or OD-H® column, *n*-hexane-isopropanol, flow 1 mL/min, on the instrument equipped with a changeable UV detector.

Sigma-Aldrich Lipase B from *Candida antarctica* (CALB) , recombinantly expressed in *Aspargilus niger* andimmobilized on acrylic resin was used further referred to as CALB. Isopropenyl acetate was used as purchased. Kinetic resolution experiments were carried out using a rotary shaker.

The catalyst $[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4COHOCC_4Ph_4)]$ (**1**), ruthenium chloride cymene dimer $[Ru(cymene)Cl_2]_2$ (**4**) and *N,N,N',N'*-tetramethylpropanediamine were purchased from Aldrich. Toluene was dried by distilling from sodium-potassium alloy. Organic extracts were dried over Na_2SO_4 and the solvents were evaporated using a rotary evaporator.

Racemization of (*S*)-4-hydroxy-2-methylcyclopent-2-en-1-one (5) with catalyst 1.



In a flame dry and flashed with argon round bottom flask equipped with a condenser and an argon inlet, (*S*)-**5** (56 mg, 0.5 mmol, 98% ee), anhyd toluene (2 mL) and **1** (21.7 mg, 2 mol%)

were placed. The mixture was heated for 24 h at the temperature indicated below and then cooled and transferred into a silica gel column (3 g). Elution of the column with hexane-EtOAc, 50:50, gave a dione **6**; further elution afforded a hydroxy-ketone fraction. The composition of the hydroxy-ketone fraction was determined by HPLC (Daicel Chiralcel AD-H® column, hexane-isopropanol, 95:5). The results were as follows:

(1) at 70 °C, **6**, 23%, the hydroxy-ketone fraction, 74% yield, consisting of (*S*)-**5** (49%), (*R*)-**5** (4%) and (*R*)- and (*S*)-**7** (25% and 22%).

(2) at 100 °C, **6** (51%), the hydroxy-ketone fraction, 13% yield containing by HPLC analysis (*S*)-**5** and (*R*)-**5**, 22% and 21%, respectively, and epimers of **7** (29 and 27%).

In the ^{1}H NMR spectra of hydroxy-ketone fractions only trace signals that could correspond to secondary methyl groups appeared.

2-Methylcyclopent-2-en-1,4-dione (**6**): IR (film from $CHCl_3$) 1746, 1706, 1618 cm^{-1}; ^{1}H NMR (400 MHz) 6.99 (q, *J* = 1.2 Hz, 1 H), 2.86 (s, 2 H), 2.09 (br d, 1.2 Hz, 3 H); ^{13}C NMR (100 MHz) 201.3, 199.5, 162.5, 146.1, 41.5, 11.2; in agreement with the reported data.[15]

(*R*)- and (*S*)-4-hydroxy-3-methylcyclopent-2-en-1-one (**7**), diagnostic signals (from a mixture with **5**): ^{1}H NMR (500 MHz) 5.95 (s, 1 H), 4.79 (br d, *J* = 6.1 Hz, 1 H), 2.18 (s, 3H); ^{13}C 205.8, 177.4, 131.3, 72.5, 45.2, 15.8; in agreement with the reported data.[16]

Racemization of (*S*)-5 with [(cymene)$RuCl_2$]$_2$ complex 4 and $Me_2N(CH_2)_3NMe_2$.

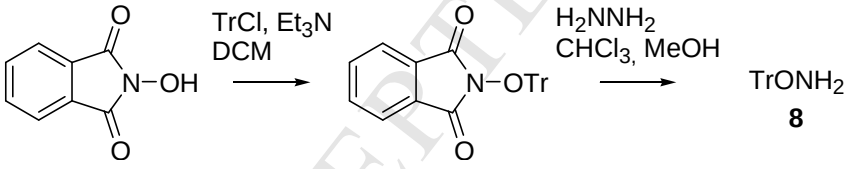
Ru-complex **4** (5.5 mg, 2 mol%) was weighted in a 5 mL cylindrical vial and then the solvent (2 mL) was added and a stirring bar introduced. The mixture was stirred for 15 min and then were added (*S*)-**5** (98% ee, 50 mg, 0.45 mmol), and *N*,*N*,*N*',*N*'-tetramethylpropanediamine (67 μL, 49 mg, 0.40 mmol, 90 mol%). The vial was placed in a oil bath at 40 ^{o}C (+/-1 ^{o}C) and the mixture was stirred. After 3 h, an aliquot was taken HPLC analysis. After 20 h, the mixture was cooled and transferred to a silica gel column (3 g). The column was eluted with

hexane-EtOAc, 50:50 to give the product (87-91% material was recovered). The composition of the product was determined by HPLC (Daicel Chiralcel AD-H® column, hexane-isopropanol, 95:5). Signal of one enantiomer of **7** partly overlapped with that of (*R*)-**5**. The results are given in Table 1.

^{1}H NMR spectra of crude products showed the presence of only traces of contaminations. (less than 5% in total)

Kinetic resolution of *rac*-5.

Experiments on kinetic resolution of *rac*-**5** were carried using CALB and IPA in TBME as reported previously.[14] It was noted that efficiency of this process depends on content of water in the solvent: in HPLC-grade commercial MTBE (water content <0.01%) or dried MTBE kinetic resolution was poor, using CALB preparation as purchased as well as that preliminary stored over saturated solution of LiCl.[5f] Using commercial MTBE or the solvent pre-equilibrated with water the previously reported results were reproduced.

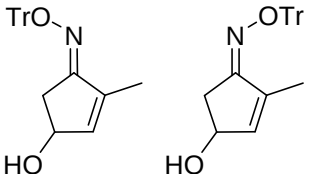


Preparation of *O*-tritylhydroxylamine (8).

Triethylamine (6.0 mL, 43.1 mmol) was added dropwise, within 5 min, to a stirred solution of *N*-hydroxylphthalimide (6.42g, 39.4 mmol) and tritylchloride (10.01 g, 35.8 mmol) in dichloromethane (55 mL). The mixture was stirred for 1 h and then poured into water (100 mL). The organic layer was separated, washed with water (2 × 100 mL) and dried. The solvent was evaporated to give *N*-(trityloxy)phthalimide (white foam, 15.54 g). This product, without purification, was dissolved in chloroform (320 mL) containing MeOH (32 mL) and then hydrazine hydrate (5.2 mL, 165.5 mmol) was added dropwise. The mixture was stirred

for 2 h and then poured into water (400 mL). The organic layer was separated, washed with water (2 × 300 mL) and dried. The solvent was evaporated and the residue was chromatographed on silica gel (100 g, hexane - EtOAc, 9:1, ca. 1 L) to give **8** (8.92 g, 90% from tritylchloride): white crystals, mp 85-86 ^{o}C (hexane); ^{1}H NMR (400 MHz): 7.47-7.43 (m, 6 H, aromatic H), 7.37-7.26 (m, 9 H, aromatic H), 4.95 (br s, 2 H, NH); ^{13}C NMR (100 MHz): 143.2, 128.8, 127.8, 127.2, 90.8.

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.98; H, 6.07, N, 5.02.



***E- and Z*-(±)-4-Hydroxy-2-methylcyclopent-2-en-1-one *O*-trityloxime (*rac*-9).**

O-Tritylhydroxylamine (5.62 g, 20.4 mmol) and AcOH (0.1 mL, 1.8 mmol) were added to a stirred solution of *rac*-**5** (2.08 g, 18.6 mmol) in MeOH (40 mL). The mixture was stirred at rt for 3 days and then the solvent was evaporated. The residue was dissolved in dichloromethane - hexane (1:1) and transferred to a silica gel column (150 g). The column was eluted with hexane – EtOAc (85:15, ca. 3 L) to give *E-rac*-**9** (white foam, 5.52 g, 81%). Further elution with hexane-EtOAc (8:2, ca. 1L) give *Z-rac*-**9** (white foam, 1.16 g, 17%).

Z-**9** partly isomerized into *E*-**9** on dissolving in $CDCl_3$.

Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.20; H, 6.37, N, 3.56.

In an analogous way from (*S*)-**6** (616 mg, 5.5 mmol) were obtained:

1. *E*-(*S*)-**9** (thick oil, 1685 mg, 83%); $[\alpha]_D^{22}$ -81.1 (c 1.50);

^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.60 (2 H, m, C2'H), 7.16 (2 H, m, C3'H), 7.08 (1 H, m, C4'H), (couplings in the aromatic protons multiplets: $^{3}J_{2',3'}$=7.9 Hz; $^{4}J_{2',4'}$=1.3 Hz; $^{4}J_{3',3'}$= 1.6 Hz; $^{4}J_{2',2'}$= 2.4 Hz; $^{5}J_{2',3'}$ = 0.5 Hz), 5.63 (1 H, dq, $^{3}J_{34}$ =2.4 Hz; $^{4}J_{36}$=1.5 Hz, C3H), 4.29 (1 H, dddq, $^{3}J_{45pro(S)}$=6.7 Hz; $^{3}J_{45pro(R)}$ =1.9 Hz; $^{3}J_{34}$ =2.4 Hz; $^{5}J_{46}$=1.3 Hz, C4H), 2.90 (1 H, dd, $^{2}J_{5pro(R)5pro(S)}$ =18.8 Hz; $^{3}J_{45Hpro(S)}$=6.7 Hz, C5Hpro(*S*)), 2.41 (1 H, dd, $^{2}J_{5pro(R)5pro(S)}$=18.8 Hz;

$^{3}J_{45pro(R)}$ =1.9 Hz, C5Hpro(*R*)), 1.49 (3 H, dd, $^{4}J_{36}$=1.5 Hz; $^{5}J_{46}$=1.3 Hz, C6H); □ ^{13}C MNR (400 MHz, C_6D_6, 25 °C) 164.23 (C1), 146.12 (C1'), 142,40 (C3), 140.72 (C2), 130.42 (C3'), 128.47 (C2'), 127.99 (C4'), 91.67 (C7), 72.83 (C4), 37.68 (C5), 12.30 (C6).

2. *Z*-(*S*)-**9** (semicrystalline mass, 303 mg, 15%); $[\alpha]_D^{23}$ -56.2 (c 1.80).

^{1}H NMR (400 MHz, C_6D_6, 25 °C) 7.69 (2 H, m, C2'H), 7.17 (2 H, m, C3'H), 7.08 (1 H, m, C4'H), (couplings in the aromatic protons multiplets: $^{3}J_{3'4'}$=7.3 Hz; $^{3}J_{2'3'}$=7.9 Hz; $^{4}J_{2'4'}$= 1.3 Hz; $^{4}J_{3'3'}$= 1.6 Hz; $^{4}J_{2'2'}$= 2.4 Hz; $^{5}J_{2'3'}$=0.5 Hz), 5.70 (1 H, dq, $^{3}J_{34}$ =2.3 Hz; $^{4}J_{36}$=1.4 Hz, C3H), 4.11 (1 H, dddq, $^{3}J_{45pro(S)}$ = 6.9 Hz; $^{3}J_{45a}$ = 2.6 Hz; $^{3}J_{34}$ = 2.3 Hz; $^{5}J_{46}$=1.6 Hz, C4H), 2.57 (1 H, dd, $^{2}J_{5pro(R)5pro(S)}$ = 17.1 Hz; $^{3}J_{45pro(S)}$ =6.9 Hz, C5Hpro(*S*)), 2.27 (3 H, dd, $^{4}J_{36}$= 1.4 Hz; $^{5}J_{46}$=1.6 Hz, C6H); 2.08 (1 H, dd, $^{2}J_{5pro(R)5pro(S)}$ = 17.1 Hz; $^{3}J_{45pro(R)}$ =2.6 Hz, C5Hpro(*R*)); δ ^{13}C NMR (400 MHz, C_6D_6, 25 °C) 159.86 (C1), 147.00 (C3), 146.16 (C1'), 138.74 (C2), 130.51 (C3'), 128.51 (C2'), 127.98 (C4'), 92.41 (C7), 71.57 (C4), 40.92 (C5), 18.77 (C6).

Experimental and DFT calculated chemical shifts for *E*- and *Z*-**9** in benzene are compiled in Table 6. Discussion on chemical shift calculations are presented in the Supporting Information.

Isomerization of *Z*-*rac*-9 into *E*-*rac*-9.

Z-*rac*-**9** (40 mg, 0.11 mmol) was dissolved in DCM (1.5 mL) and a solution HCl in DCM was added (0.01 mL) [prepared by adding TMSCl (0.17 mL, 1.37 mmol) and MeOH (0.06 mL, 1.44 mmol) to DCM (10 mL)]. The mixture was stirred at rt for 5 min and the solvent was evaporated to give *E*-*rac*-**9** (40 mg, 100%).

Z-*rac*-**9** was recovered unchanged after heating in toluene for a few hours; heating in xylene resulted to the substrate decomposition.

Kinetic resolution of *rac*-*E*-9, general conditions

To a solution of *rac*-*E*-**9** in a solvent, containing IPA (3 mol equiv), CALB (10% w/w) was added and the mixture was shaken at ambient temperature (20 – 25 ºC). Progress of reaction was followed by HPLC. After the reaction was completed, the solid was filtered off and the

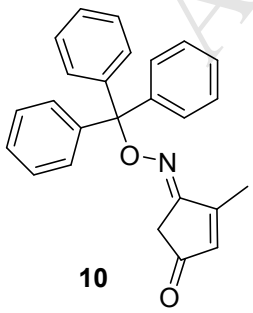
solvent, and the volatiles were removed on a rotary evaporator. The residue was chromatographed on a silica gel column to afford the product. Average *E* values were calculated from a series of consecutive measurements accordingly to the standard protocol.[20] The results are combined in Table 2.

HPLC, ODH Chiralcel column, hexane – isopropanol, 94:6, R_t (min): (*S*)-*E*-**9**-acetate, 4.85; (*R*)-*E*-**9**-acetate, 6.79; (*R*)-**9**, 10.04; (*S*)-**9**, 12.36 . (R_t values depended upon degree of the column worn out.)

Racemization of (*S*)-*E*-9, general conditions

Catalyst **4** was weighted in a 10 mL vial (3.40-3.70 mg). A magnetic stirring bar, DCE (4 mL) and (*S*)-*E*-**9** (98% ee), ca. 100 mg, as calculated taking 2 mol% of **4**, were added. The vial was placed in an oil bath preheated to 40 °C and mixture was briefly stirred (ca. 5 min, until the solid was dissolved) and then *N,N,N',N'*-tetramethylpropylidenediamine (36 μL, 0.8 mol equiv) was added by a syringe. Stirring at 40 ºC was continued while samples were taken from the mixture and applied to the HPLC column fitted with a pre-column. The side product was identified as the oxo-derivative **10** by comparison with a sample was prepared as described below. The results are shown in Table 3.

In an analogous way experiments using (*S*)-*E*-**9,** catalyst **4** and triethylamine (0.8 mol equiv) in DCE were carried out. The results are shown in Table 4.



10

Preparation of *E*-2-methylcyclopent-2-en-1,4-dione 1-*O*-trityloxime (10).

Dess-Martin periodinane (150 mg, 0.35 mmol) was added to a solution of (*S*)-*E*-**9** (109 mg, 0.30 mmol) in DCM (4 mL). The mixture was stirred for 0.5 h and then poured into $NaHCO_3$ solution and extracted with EtOAc (20 mL). The extract was washed consecutively with Na_2SO_3 solution, water and brine, and dried (Na_2SO_4). The solvent evaporated and the product was chromatographed on silica gel (3 g, 10% EtOAc in hexane) to give **10** (106 mg, 97% yield): mp 148 ºC (hexane); IR (film from CH_2Cl_2) 1716 cm^{-1}; ^1H NMR (500 MHz) 7.35-7.24 (m, 15 H, aromatic H), 6.24 (s, 1H, =C-H), 3.22 (s, 2 H, -CH_2-), 1.99 (s, 3 H, Me); ^{13}C NMR (125 MHz) 201.0, 165.4, 157.1, 144.0, 135.9, 129.2, 127.6, 127.3, 91.9, 35.8, 13.2. Elemental analysis $C_{25}H_{21}NO_2$ (367.45) calcd C, 81.72, H, 5.76, N, 3.81; found C, 81.71, H, 5.62; N, 3.74.

Dynamic kinetic resolution of *rac*-9, general conditions

One-stage procedure: Alcohol *rac*-*E*-**9** (55 mg), CALB (10 or 20 %, w/w), DCE (2 mL) and IPA (52 μL) were placed in a 5 mL vial equipped in a magnetic stirring bar. To the stirred mixture were added consecutively: 0.5 mL of a solution of **4** in DCE [prepared by dissolving **4** (3.4 mg) in DCE (1 mL)] and Et_3N (15 μL). The vial was placed in a preheated oil bath (at 40 or 60 ºC) and stirring was continued. Samples were taken from the mixture and applied to the HPLC column fitted with a pre-column.

Two-stage procedure was carried out in the same way except that the addition of a solution of the catalyst **4** and Et_3N was delayed by the indicated period of time. The results are given in Table 5.

Preparative scale experiment: In a 25 mL round-bottomed flask with a magnetic stirring bar there were placed: *rac*-*E*-**9** (307 mg, 0.83 mmol), CALB (30 mg) and DCE (12 mL). The mixture was briefly stirred at rt and then IPA (0.27 mL, 2.45 mmol) was added and the flask was sealed with a glass stop cork and placed in a pre-heated oil bath at 40 ºC. After 48 h, a

sample was taken and the composition of the mixture was determined by HPLC as: (*S*)-*E*-**9**-acetate, 37.10%, (*R*)-*E*-**9**-acetate, 0.34%, (S)-*E*-**9**, 49.91%, (*R*)-*E*-**9**, 12.65%. At this point catalyst **4** (10.1 mg, 0.0165 mmol) and Et_3N (0.09 mL, 0.64 mmol) were consecutively added and stirring was continued for an additional 5 days. The composition of the mixture determined by HPLC was as follows: (*S*)-*E*-**9**-acetate, 82.59%, (*R*)-*E*-**9**-acetate, 0.64%, (*S*)-*E*-**9**, 4.82%, (*R*)-*E*-**9**,* 3.53%, **10*** 8.41% (*picks partly overlapping). After further 3 days (8 days in total) composition of the mixture was as follows: (*S*)-*E*-**9**-acetate, 86.42%, (*R*)-*E*-**9**-acetate, 0.60%, (S)-*E*-**9**, 2.82%, (*R*)-*E*-**9** and **10** 10.75%.

The solid was then filtered off and the solvent, and volatiles were evaporated. The residue was transferred to a silica gel column (50 g) and the column was eluted with EtOAc : hexane, 5:95 (1.3 L) to give: (*S*)-*E*-**9**-acetate (288 mg, 84%, 97.4% ee) and **10** (43 mg, 14%) [ODH Chiralcel column, hexane – isopropanol, 94:6, R_t 11.34 min.]

(*S*)-*E*-**9**-acetate: ^{1}H NMR (500 MHz) 7.35-7.21 (m, 15, aromatic H), 6.12 (s, 1 H, =C-H), 5.65 (br d, *J* = 5.9 Hz, 1 H, C4-H), 3.27 (dd, *J* = 18.8, 6.9 Hz, 1 H, CH_{2A}), 2.72 (br d, *J* = 18.8, CH_{2B}), 2.05 (s, 3 H, $OCOCH_3$), 1.68 (br s, 3H, Me); ^{13}C NMR (125 MHz) 170.8, 162.0, 144.5, 143.3, 136.4, 129.2, 127.4, 127.0, 90.6, 74.6, 33.7, 21.1, 11.7.

Acknowledgements

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Supporting Information.

Copies of ^{1}H and ^{13}C spectra of compounds **8**, *E*-**9**, *Z*-**9**, and **10**; *E*-**9**, *Z*-**9,** details of NMR experiments and *ab initio* calculations.

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Tables

Table 1.

	Solvent[a]	T (h)	Recov. %[b]	(*ee*%)	Δ*ee*[c] (%)	**7%**[d]
1	MTBE	3	-	88	10	-
2		20	88	54.	44	1
3	Tol	3	-	48	50	1
4		20	91	5	93	5
5	ClPh	3	-	43	55	1
6		20	87	3	95	5
7	DCE	3	-	29	69	1
8		20	88	0	98	6
9	DCE[e]	20	-	0	98	6
10	DCE[f]	20	-	98	0	-

Table 2.

	Solvent[a]	T (h)	Conv. (%)	(*S*)-OAc *ee*%	(*R*)-OH *ee*%	E[b]
	Tol	2	10	87	9	
		20	51	74	80	16
	ClPh	2	6	92	6	
		20	40	86	44	23
		44	53	79	88	
	DCE	2	.4	98	4	
		20	24	98	30	158
		44	38	98	58	
		72	44	97	76	
		5d	50	96	95	

Table 3.

Solvent[a]	Time	(*S*)-OH, *ee*%	Δ*ee*[b]	Ketone **10**, **%**
DCE	5 min	37	61	3
	15 min	25	73	3
	30 min	23	75	3
	1 h	18	80	4
	2 h	14	84	4
	3 h	14	84	5
	24 h	5	93	5
DCE acetone 3 eq	5 min	22	76	4
	15 min	7	91	7
	30 min	4	93	8
	1 h	2	96	9
	2 h	1	97	10
Tol	3 h	27	71	4

	24 h	14	84	8
PhCl	3 h	11	86	3
	24 h	7	91	8

Table 4.

Time	Propylidenediamine[a]			Et_3N		
	ee%	Δ*ee*	**10**(%)	*ee*%	Δ*ee*	**10**(%)
5 min	37	61	3	39	60	3
15 min	25	73	3	33	65	3
30 min	23	75	3	30	68	4
1 h	20	78	4	26	72	5
2 h	16	82	4	23	75	5
3 h	12	86	4	22	76	6
22 h	7	91	7	18	80	10

Table 5.

	1st Stage		2nd Stage		Total time (days)	CALB (%w/w)	(*S*)-*E*-**9**-acetate,[b] %, (*ee*%)	Alcohols(%) (*R*/*S* ratio)[c]	Ketone **10** (%)
	Temp. (ºC)	Time (days)	Temp. (ºC)	Time (days)					
1	40	3	-	-	3	10	61 (>98)	32 (2/1)	7
2	40	6	-	-	6	10	75 (>98)	17 (2/1)	8
3	40	10	-	-	10	10	82 (>98)	8 (2/1)	10
4	60	3	-	-	3	10	66 (97)	11 (1/1)	23
5	40	3	-	-	3	20	76 (97)	18 (5/1)	5
6	40	6	-	-	6	20	88 (97)	7 (5/1)	6
7	40	2[d]	40	5	7	10	85 (>98)	8 (5/3)	8
8	40	3[e]	40	7	10	10	85 (97)	7 (5/2)	8
9	40	1[f]	40	5	6	20	88 (98)	6 (4/1)	7
10	60	1[g]	60	3	4	20	84 (95)	5 (2/1)	11

Table 6.

#	δ^{13}C /ppm					
	experimental			calculated		
	Z-**9**	*E*-**9**	$\Delta\delta^{Z}_{E}$	*Z*-**9**	*E*-**9**	$\Delta\delta^{Z}_{E}$
1	159.22	164.23	**-5.01**	167.51	169.82	**-2.31**
2	138.10	140.72	**-2.62**	146.17	146.06	**0.11**
3	146.36	142.40	**3.96**	148.03	145.83	**2.20**
4	70.93	72.83	**-1.90**	70.47	72.54	**-2.07**
5	40.28	37.68	**2.60**	39.36	37.37	**1.99**
6	18.13	12.30	**5.83**	15.41	7.97	**7.44**
7	91.77	91.67	**0.10**	91.56	90.95	**0.61**
1′	145.52	146.12	**-0.60**	148.51	148.14	**0.37**
2′	127.87	128.47	**-0.60**	131.16	130.95	**0.21**
3′	129.87	130.42	**-0.55**	127.86	127.9	**-0.04**
4′	127.34	127.99	**-0.65**	126.85	127.27	**-0.42**

Legends to Tables

Legend to Table 1.

[a]Abbreviations: MTBE – tert-butyl methyl ether, Tol – toluene, ClPh – chlorobenzene, DCE – 1,2-dichloroethane.
[b]The product was isolated and purified by chromatography after 20 h; intermediate measurements were carried out on samples taken from the reaction mixture.
[c]Racemization capacity,[9] $\Delta ee = ee_0 - ee_t$.
[d]Content in the mixture, HPLC signal of one enantiomer of **7** partly overlapped with that of (R)-**5**.
[e]Added acetone, 3 mol equiv.
[f]Added acetic acid, 3 mol equiv.

Legend to Table 2.

[a]Solvent name abbreviations are as in Table 1.
[b]E values were calculated accordingly to the literature protocol.[20]

Legend to Table 3.

[a]Solvent name abbreviations are as in Table 1.
[b]Racemization capacity,[9] $\Delta ee = ee_0 - ee_t$.

Legend to Table 4.

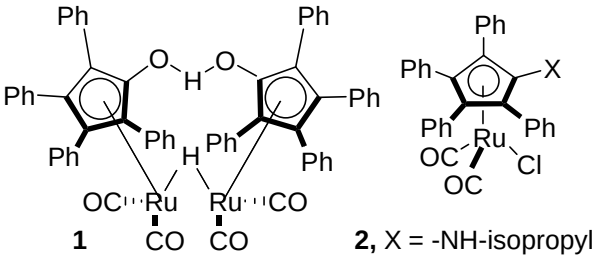
[a]*N,N,N',N'*-tetramethylpropylidenediamine.

Legend to Table 5.

[a]The experiments were conducted in ca. 0.15 mmol scale [ca. 50 mg of (S)-E-**9]**, in DCE solution (5%) with magnetic steering, using CALB (as indicated), IPA (3 mol equiv), catalyst **4** (2 mol%) and triethylamine (0.8 mol equiv).
[b]Average of at least 3 measurements.
[c]The less mobile alcohol enantiomer partly overlapped with the ketone on HPLC analysis.
[d]Content of **9**-acetates (S/R) as 37.1/0.3%.
[e]Content of **9**-acetates (S/R) as 44.8/0.6%.
[f]Content of **9**-acetates (S/R) as 35.6/0.3%.
[g]Content of **9**-acetates (S/R) as 47.1/1.3%.

Figures

Figure 1.



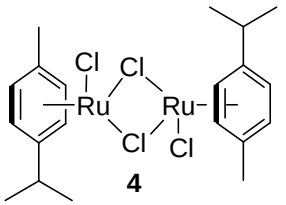
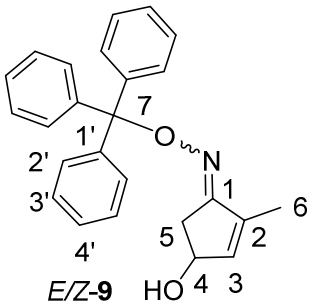
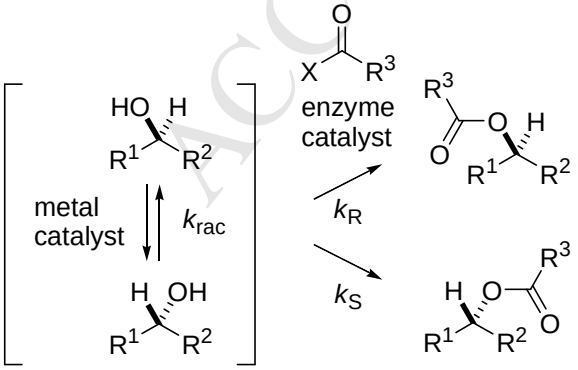


Figure to Table 6.

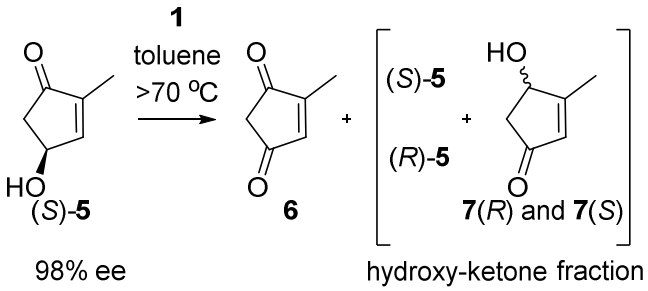


Schemes

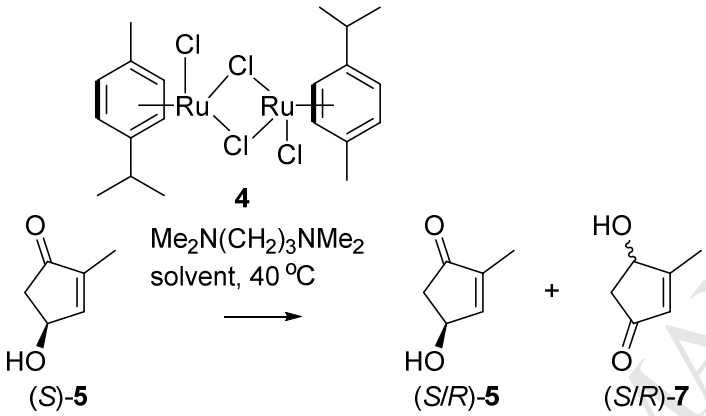
Scheme 1.



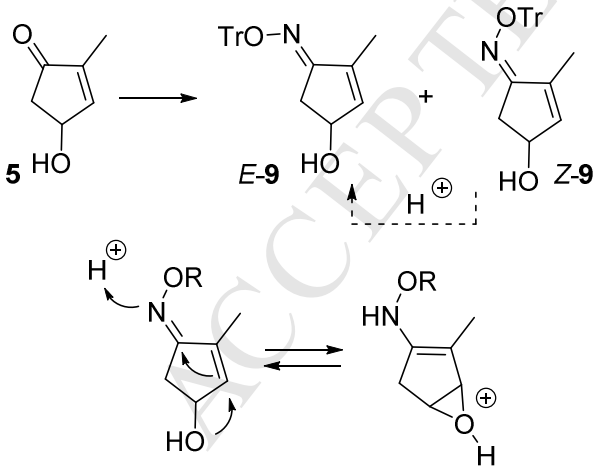
Scheme 2.



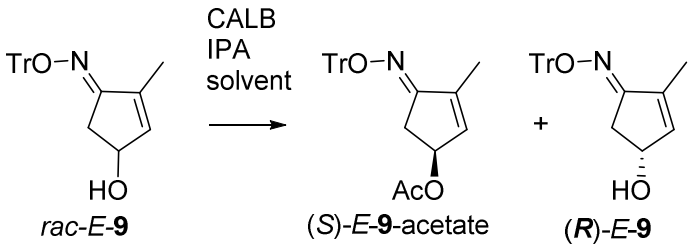
Scheme to Table 1.



Scheme 3.

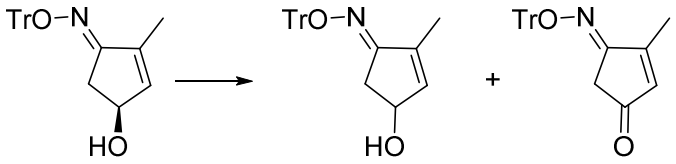


Scheme to Table 2.



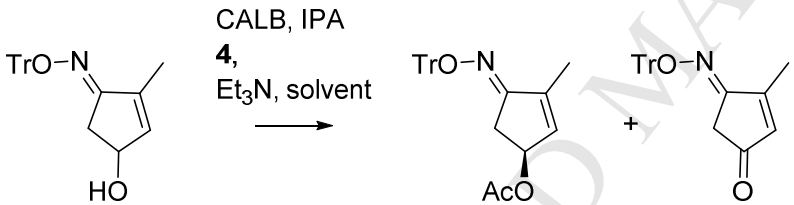
rac-E-**9** (*S*)-*E*-**9**-acetate (***R***)-*E*-**9**

Scheme 4.



(S)-*E*-**9** *(R/S)*-*E*-**9** **10**

Scheme to Table 5.



rac-E-**9** (*S*)-*E*-**9**-acetate **10**