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A Practical Chemo-enzymatic Synthesis of Homochiral Bicyclo[2.2.2]octane-2,5-dione

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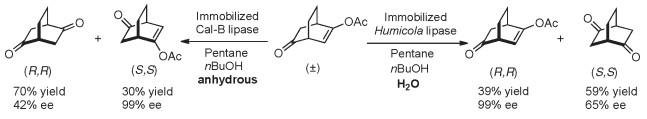
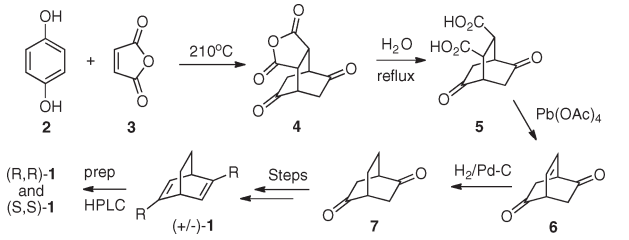


A practical synthetic route for the preparation of chiral bicyclo[2.2.2]octane-2,5-dione, the precursor of useful chiral diene ligands, was realized via Diels−Alder reaction and resolution of an enol acetate derivative by immobilized lipases.

Chiral diene ligand complexes[1] of rhodium are highly effective catalysts for the asymmetric addition of arylboronic acids to α,β-unsaturated ketones,[2] asymmetric arylation of *N*-tosylarylamines,[3] arylative cyclization of alkynals,[4] and intramolecular asymmetric [4 + 2] cycloaddition of alkyne-1,3,-dienes.[5] Complexes with iridium are used for resolution of allyl carbonates.[6] The C_2-symmetric 2,5-disubstituted bicyclo[2.2.2]octane-2,5-dienes **1** developed by Hayashi (Scheme 1) have shown particular versatility. The bicyclic 2,5-diene is also a starting material for synthesis of CNS-modulators.[7] The chiral diketones **7**, synthetic precursors to

SCHEME 1. Existing Synthetic Route to Chiral Diene Ligands 1



the diene compounds, are difficult to access both in terms of synthesis and resolution and this may have limited widespread application of chiral diene ligands in asymmetric catalysis. For the synthesis of racemic **7**, the most frequently used route (Scheme 1) is low yielding (overall 4%): Diels−Alder reaction of hydroquinone **2** with maleic anhydride **3** gives compound **4**, which upon hydrolysis gives the diacid **5**. The decarboxylation step affords compound **6** in low yield (14%) which is then hydrogenated to give compound **7**.

A number of approaches have been taken for resolution of the diketone or its synthetic prescursors. The unsaturated dione **6** has been resolved as diastereomeric diethyl (*R*,*R*)-(+)-tartrate acetals[8] and as an inclusion complex with (*S*)-(−)-(10,10′)-dihydroxy-9,9-biphenanthryl,[9] and the diacid **5** was resolved as its brucine salt, followed by electrolysis to give (−)-**6**.[8,10] Furthermore a chiral dihydrazone of compound **7** was resolved by fractional recrystallization.[2a] However, all these methods were inefficient for multigram preparation.

Naemura investigated resolution of bicyclo[2.2.1]heptane-, bicyclo[2.2.2]octane-, and bicyclo[3.2.1]octanediols by lipase-catalyzed transesterification or hydrolysis reactions. The best result for the hydrolysis of the diacetate of *endo*,*endo*-2,5-dihydroxybicyclo[2.2.2]heptane was 29% yield and 84% ee.[11a] The lipase YS catalyzed transesterification on the diols was only successful for the [3.3.1] system and gave no improvement for the [2.2.2] system.[11b] Racemic diketone **6** was resolved by baker's yeast reduction to give hydroxyketone and unreacted (+)-ketone **6** with varying ee's depending on the incubation time.[10] Frejd et al. developed a route to chiral diketone **7** using a 1,2-carbonyl transposition starting from (1*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one in nine steps.[12a] One notable result has been reported by the same group recently: compound **7** was reduced to a diastereomeric

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mixture of hydroxy ketones in 98% conversion and 99% ee for each diasteroisomer by using genetically engineered *Saccharomyces cerevisiae*.[12b] However, this approach suffered from low substrate concentrations and separation problems. In practice, the homochiral diene ligands are prepared by preparative chiral HPLC resolution (Chiralcel OJ) of the diketone, the diene, or a bis enol triflate intermediate.[2a]

We have been exploring alternative synthetic routes and resolution methods for accessing diketone **7** in order to make the diene ligands and thus the asymmetric transformations more accessible to the synthetic community. Herein, we provide a practical chemoenzymatic route to homochiral diketone **7**. The key step is a lipase-catalyzed resolution of the (±)-enol acetate **13**, derived from the diketone **7** (Scheme 2). Solvent screening, choice of immobilization material, and optimization of reaction conditions has resulted in the indentification of enantiocomplementary biotransformations to access either enantiomer of diketone **7** in homochiral form.

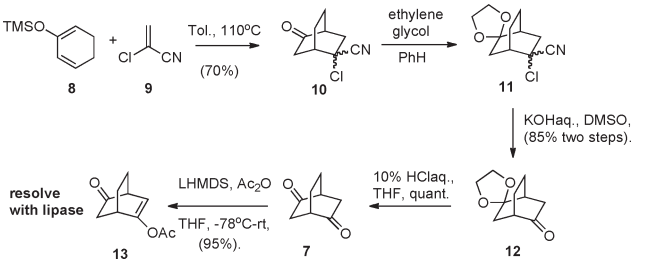
The bicyclic [2.2.2] system was constructed by [4 + 2] cycloaddition of 2-(trimethylsiloxy)-1,3-cylcohexadiene **8** and 2-chloroacrylonitrile **9**.[12c] The major product was the desired 2,5-adduct **10**, after cleavage of the intermediate enol silyl ether which apparently occurs in situ. The ketone group in compound **10** was protected with ethylene glycol to give **11** prior to hydrolysis to afford the monoacetal **12**[13] (two steps 85% yield). Hydrolysis of the ketal group with 10% HCl/THF at room temperature afforded racemic diketone **7** in quantitative yield. This route thus provides the diketone **7** in an overall 60% yield for four steps.

We have previously developed lipase-catalyzed resolutions of enol acetates as an effective alternative to asymmetric enolate formation for the desymmetrisation of prochiral ketones (Scheme 3).[14] The enol acetate **14** was resolved with *Pseudomonas fluorescens* lipase (PFL) to provide a key building block for the synthesis of NK-2 antagonists.[15] Similarly oxabicyclic enol ester **15** was resolved with high selectivity using silica-absorbed *Humicola* sp. lipase.[16]

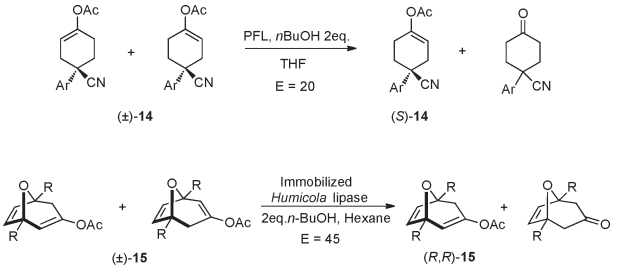
Thus, we envisioned a resolution of enol acetate **13** as a way of obtaining optically pure diketone **7**. Our previously employed PFL in THF gave no reaction, while silica-absorbed *Humicola* sp. lipase in hexane gave low selectivity. An initial screen of lipases was carried with various solvents. Only *Candida antarctica* lipase (Cal-B) showed moderate enantioselectivity in toluene ($E = 15$), albeit with a very low reaction rate.

Given our earlier success with immobilized *Humicola* sp. lipase for the bicyclic compound **15**, investigation was focused on this enzyme (Table 1). Solvent screening showed that the silica-absorbed *Humicola* sp. lipase[16] works best in hydrophobic solvents, with pentane giving the highest initial E value of 15 (entry 5). The lyophilized enzyme gave lower selectivity although this could be improved by the presence of a small amount of water (5 equiv) (entry 6 vs 7). The commercially supplied enzyme in phosphate buffer gave very

SCHEME 2. Preparation of Bicyclo[2.2.2]octane-2,5-dione 7 and Corresponding Enol Acetate 13



SCHEME 3. Lipase-Catalyzed Resolution of Cyclic Enol Acetates



low selectivity (entry 8). Use of the protein-coated microcrystal prepared according to Kreiner[17] led to an increased rate of conversion but lower selectivity (entry 9).

Exciting results were obtained with the enzyme immobilized on the hydrophobic supports Accurel[18] or PhosES-03 (PhosphonicS) in pentane (entries 13 and 14), where the E values were as high as 68 and 116, respectively. This high selectivity depended on the presence of residual water in the immobilized enzyme from the immobilization process. Accurel is polypropylene powder with ca. 250 μm particle size, with a large hydrophobic surface to which the enzyme adsorbs; PhosES-03 is functionalized silica with a high degree of hydrophobic surface modification and covalent linkage to the enzyme.

Silica, sol−gel,[19] and PhosES-01 (entries 5, 10, and 11) all contain no surface modification and gave lower E values than entries 13 and 14. The supporting silica PhosES-02 (entry 12) is partially modified (less than PhosES-03) with surface hydrophobic groups, and in this case, the E value of 40 was intermediate between entries 5, 10, 11 and entries 13 and 14. Interestingly, the widely used Eupergit[19] support gave disappointing selectivity (entries 16 and 17), which may be explained by the relatively polar amino alcohol residues generated at the point of enzyme attachment to the resin. These results indicate that the more hydrophobic the support surface, the better the enantioselectivity of the enzyme for this biotransformation. This could be attributed to a conformational change within the active site. Biophysical studies using solid-state IR spectroscopy indicate that the hydrophobic lid that covers the active site of *Humicola* sp. lipase is

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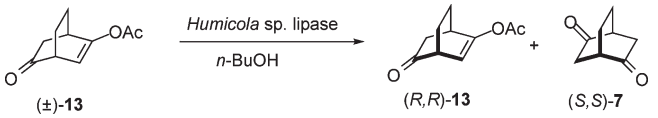
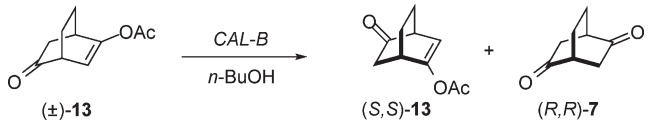
TABLE 1. Screening *Humicola* sp. Lipase



entry[a]	solvents	immobilization	conversion[i] (%)	(R,R)-enol ester 13 ee[j] (%)	reaction time	*E* value
1	hexane	silica[g]	60	73	2 d	6
2	cyclohexane	silica[g]	31	28	1 d	5
3	heptane	silica[g]	29	27	1 d	6
4	petroether	silica[g]	27	26	1 d	5
5	pentane	silica[g]	31	37	1 d	15
6[b]	pentane	lyophilized[g]	42	45	6 d	6
7[b]	pentane	lyophilized[h]	14	15	4 d	27
8	buffer	enzyme soln	24	13	2 d	< 1
9[c]	pentane	PCMC[g]	29	31	0.5 d	10
10[d]	pentane	sol−gel[g]	29	37	3 d	29
11[e]	pentane	PhosES-01[h]	25	30	1 d	25
12[e]	pentane	PhosES-02[h]	34	48	10 h	45
13[e]	**pentane**	**PhosES-03**[h]	21	26	30 h	**116**
14[f]	**pentane**	**Accurel**[h]	30	41	3 h	**68**
15[f]	pentane	Accurel[g]	52	90	5 h	33
16	pentane	Eupergit[h]	30	22	3 d	4
17	pentane	Eupergit[g]	34	40	2 d	12

[a]Reactions were carried as follows: 10 mg of substrate, 5 equiv of *n*-BuOH, and 5 mL of solvent. For each immobilized enzyme reaction, 50 μL of enzyme solution (NaPi buffer pH 7, 100,000U/mL) was used. For silica, 200 mg immobilized catalyst X 2 was used in each assay; for the PhosES series, 100 mg immobilized catalyst X 2 was used for each assay. [b]2 mg of freeze-dried enzyme was used. [c]Protein coated microcrystal method ref 17. [d]Reference 19. [e]PhosES01-03 were silica materials given by Phosphonics, Ltd. [f]Accurel adsorption: ref 18. [g]Dry catalyst. [h]Catalyst containing water (see the Experimental Section); for entry 7, 5 equiv of water with respect to substrate added. [i]conversion determined by GC. [j]Ee of enol ester **13**, determined with chiral HPLC on Chiracel AD column.

TABLE 2. Screening CAL-B Lipase



entry[a]	solvents	immobilization	conversion (%)	(S,S)-enol ester 13 ee[d] (%)	reaction time	*E* value
1	buffer	lyophilized[b]	55	69	12 h	7
2	hexane	lyophilized[b]	65	60	7 d	3
3	toluene	lyophilized[b]	54	78	5 d	11
4	toluene	silica[b]	57	85	5 d	12
5	pentane	PCMC[b]	58	85	30 h	11
6	pentane	Sol−gel[b]	12	11	3 d	10
7	pentane	PhosES-01[c]	21	21	2 d	11
8	pentane	PhosES-02[c]	17	17	2 d	13
9	pentane	PhosES-03[c]	18	20	2 d	26
10	pentane	PhosES-03[b]	34	43	1 d	17
11	pentane	Accurel[c]			3 d	
12	**pentane**	**Accurel**[b]	**29**	**40**	**3 d**	**142**
13	pentane	Eupergit[c]	29	25	5 d	5
14	pentane	Eupergit[b]			5 d	

[a]The reaction protocols are the same as that for *Humicola* lipase when the same supporting material was used. [b]Dry catalyst. [c]Catalyst containing water. [d]Ee of enol ester **13**, determined with chiral HPLC on Chiracel AD column.

in the open conformation at the water−hydrophobic interface.[20] Surface-associated water seems to be essential for high selectivity in our reactions. This may facilitate such a conformational change resulting in increased reactivity and selectivity. If we compare entry 6 with 7 and entry 14 with 15, it can be seen that with free enzyme (entries 6 and 7) or immobilized enzyme (entries 14 and 15), a small amount of water is advantageous: entry 7 is better than 6, and 14 is better than 15.

A similar strategy was applied using Cal-B lipase (Table 2) which catalyzed the reaction with the opposite sense of enantioselectivity giving (*R,R*)-diketone **7** and unreacted (*S,S*)-**13**. Preliminary solvent screening for the lyophilized Cal-B suggested that the best organic solvent was toluene; however, there was no obvious improvement in both

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activity and enantioselectivity after immobilization on silica (cf. entries 3 and 4). Marginal improvements in selectivity were observed when using the PhosES supports in the presence of water. However, a striking increase in selectivity (entry 12, $E = 142$) was noted with Accurel under anhydrous conditions.[21] As with the *Humicola* enzyme, the Eupergit support provided no advantage for this reaction system.

On a preparative scale, use of Accurel-supported *Humicola* lipase provided the most practical method. Starting with 9 g of (±)-enol acetate **13**, we obtained 3.5 g (39%) of enantiopure (*R,R*)-**13** (>99% ee) after 50 h reaction time. The reaction is easy to follow by chiral HPLC allowing optimal recovery of enantiomerically enol ester. The (*S,S*)-diketone **7** was obtained in 59% yield, 65% ee. Immobilized Cal-B on Accurel afforded 30% isolated yield of the antipodal homochiral (*S,S*)-**13**, although the reaction time was considerably longer (18 days). Either enantiomer of the chiral diketone **7** was made in quantitative yield using *Candida rugosa* lipase in buffer to hydrolyze the enol acetate. This lipase was conveniently found to be completely nonselective for either enantiomer of **13**.

In summary, we report an efficient chemoenzymatic approach to homochiral bicyclo[2.2.2]octane-2,5-dione **7**, a key intermediate for the Hayashi diene ligand, precluding the requirement for using preparative chiral HPLC. This method includes a practical 4-step synthetic route for the racemic diketone (60% overall yield) and an enzymatic resolution, in which the racemic diketone **7** is first converted into corresponding mono enol acetate **13** for the lipase-catalyzed resolution. Immobilized lipase *Humicola* sp. lipase and Cal-B lipase gave the enol acetate with enantiocomplementary selectivity and the homochiral diketone **7** is obtained in quantitative yield by hydrolysis with *Candida rugosa* lipase.

Experimental Section

Catalyst Preparation (*Humicola* sp. Lipase on Accurel). In a small sample tube, Accurel (1 g) was vortexed with EtOH (3 mL), allowed to stand for 15 min, and then transferred to a 100 mL conical flask. Sodium phosphate buffer (0.1M, pH 6.0) (20 mL) and *Humicola* sp. lipase solution (200 μL) were added, and the resulting suspension was incubated at 30 °C for 48 h. The mixture was filtered through a Buchner funnel and washed with distilled water (3 × 2 mL). The water saturated Accurel-lipase (3 g) was then ready for use (generally 1 g of Accurel can hold ca. 2 g water). If the catalyst is not used immediately, it should be stored in a tightly stoppered sample tube in the fridge (4 °C). Before use, the catalyst should be vortexed for several minutes to encourage any water condensed on the wall of sample tube back into the catalyst. The dry catalyst was prepared by suction filtration, incubation at 30 °C for 1 day followed by drying under vacuum overnight.

Catalyst Preparation (Humicola Lipase on PhosphonicS PhosES-03). To a 100 mL conical flask containing NaPi buffer (25 mM, pH 7.0, 20 mL), PhosphonicS PhosES-03 (1 g), and *Humicola* sp. lipase solution (200 μL) was added. The resulting suspension was incubated at 30 °C for 12 h. The same workup procedure as for Accurel was applied to this mixture to give ca. 1 g of catalyst (the PhosES-03 itself contains about 40 wt % water). Storage and usage of the catalyst was as for the Accurel catalyst described above.

The same procedures were applied for immobilization of Cal-B except that 10 mg of freeze-dried CAL-B was used in place of the *Humicola* sp. lipase solution. The dry catalysts were prepared by suction filtration, incubation at 30 °C for 1 day followed by drying under vacuum overnight.

PhosES-03-Supported *Humicola* sp. Lipase-Catalyzed Resolution. Racemic enol acetate **13** (1.0 g, 5.55 mmol) was dissolved in pentane (200 mL). To this mixture was added wet *Humicola* sp. lipase on PhosES-03 enzyme catalyst (1 g) (see above) followed by *n*-BuOH (10 mmol, 740 mg). The reaction finished after 1 day. The reaction was run several times and the yield of enantiomerically pure (*R,R*)-(+)-**13** varied from 320 mg to 400 mg (32- 40% yield) with 68−60% yield of diketone−**7** obtained, after chromatography (hexane/EtOAc 4:1).

Accurel-Supported CAL-B Lipase-Catalyzed Resolution. Racemic enol acetate **13** (1.0 g, 5.55 mmol) was dissolved in pentane (200 mL). To this mixture 1 g of wet type CAL-B on Accurel (see above) was added followed by *n*-BuOH (10 mmol, 740 mg). The reaction finished after 18 d. The reaction was run several times, and the yields of enantiomerically pure (*S,S*)-(−)-**13** varied from 280 to 300 mg (28−30% yield), with 72−70% yield of diketone−**7**, obtained after chromatography (hexane/EtOAc 4:1).

Large-Scale Resolution of (±)-13 Using Accurel-Supported *Humicola* sp. Lipase. A solution of (±)-2-acetoxybicyclo-[2.2.2]octan-2-en-5-one **13** (9.0 g, 50 mmol), *n*-butanol (3.7 g, 50 mmol), and pentane (1.8 L) was added to a 3 L reactor (see the Supporting Information) in which the immobilized enzyme (made using 8 g of Accurel, see above) was placed on a fabric-covered mesh, alongside anhydrous sodium bicarbonate (2.1 g, 20 mmol) to trap any acetic acid produced. The reaction was stirred for 50 h until the (*R,R*)-enol acetate **13** was >99% ee. The reaction mixture was filtered through cotton wool to remove the immobilized enzyme and bicarbonate. After removal of the solvents, the residue was separated by silica-gel column chromatography (hexane−EtOAc 4:1) to give the enantiomerically pure (>99% ee) (*R,R*)-enol acetate **13** (3.5 g, 39% yield) and (*S,S*)-diketone−**7** (4.1 g, 59.5% yield, 64% ee).

(*R,R*)-(-) and (*S,S*)-(+)-Bicyclo[2.2.2]octane-2,5-dione 7. To a 100 mL flask containing 100 mg of (*R,R*)-(+)-**13** was added 50 mL of NaPi buffer (0.1 M, pH 7.5) and 5 mg of crude *Candida rogusa* lipase (Lipase AY). The resulting mixture was stirred for 2 h. The buffer solution was extracted with EtOAc (50 mL × 3). The combined organic extracts were dried over magnesium sulfate followed by filtration and evaporation to give pure (*R,R*)-(−)-**7** (76 mg, 100%) as a white solid: $[\alpha]^{20}_D = -43$ (*c* 0.42, $CHCl_3$). The same procedure was used to give (*S,S*)-(+)-**7**: $[\alpha]^{20}_D = +44$ (*c* 0.36, $CHCl_3$).

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Supporting Information Available: Experimental details and compound data. This material is available free of charge via the Internet at http://pubs.acs.org.

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