Kinetic Resolutions

Lipase-Catalyzed Domino Dynamic Kinetic Resolution of Racemic 3-Vinylcyclohex-2-en-1-ols/Intramolecular Diels–Alder Reaction: One-Pot Synthesis of Optically Active Polysubstituted Decalins**

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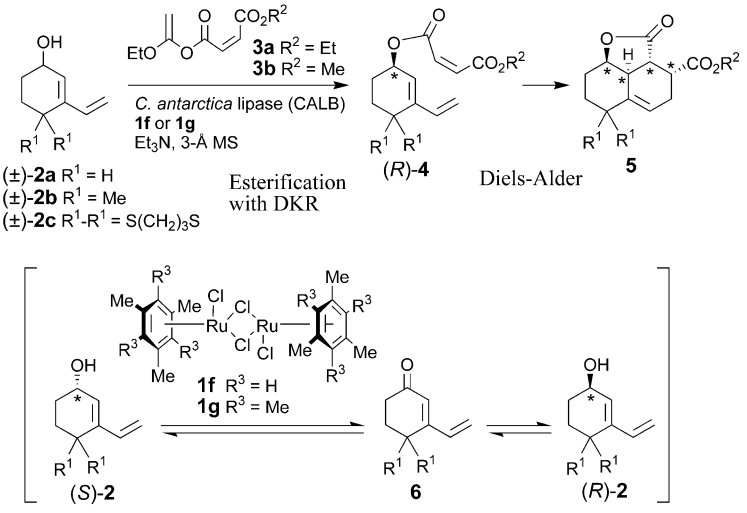
Over the past two decades the lipase-catalyzed kinetic resolution (KR) of racemic alcohols with acyl donors in organic solvents has gained increasing interest as an efficient method for the preparation of optically active compounds.[1] However, the inherent limitation of the yields to 50% at most has remained. Recently, lipase-catalyzed dynamic kinetic resolution (DKR) has been developed to overcome this problem.[2] In this reaction the KR was accompanied by the simultaneous racemization of the slow-reacting enantiomers of the alcohols with ruthenium catalysts such as [RuCl(indenyl)(PPh_3)$_2$] (**1a**),[3] [$Ru_2(CO)_4(\mu\text{-H})(C_4Ph_4COHOCC_4Ph_4)$] (**1b**),[4] [$Ru(CO)_2Cl(C_4Ph_4CNHCHMe_2)$] (**1c**),[5] [{$RuCl_2$(*p*-cymene)}$_2$] (**1d**),[6] and [$Ru_2Cl_2(\mu\text{-Cl})(\mu\text{-H})$(*p*-cymene)$_2$] (**1e**)[6] to produce optically active esters in high yields. In both the DKR and the KR, however, the installed acyl groups have seldom been utilized as part of the constituent structure for subsequent intramolecular reactions,[7] and these groups are usually removed or replaced with other groups during subsequent transformations.[4b,c] A realization of the effective use of the acyl moiety by a domino procedure[8] has been highly desired because it could minimize the use of chemicals, reduce the waste, and shorten the transformation steps.

We have recently disclosed the first example of this concept, that is, the lipase-catalyzed KR of racemic furfuryl alcohols followed by the intramolecular Diels–Alder reaction to give tricyclic products with up to 99% *ee*; however, the yields were naturally less than 50%.[9] Herein we present the first lipase-catalyzed domino process that combines the DKR of racemic alcohols **2** by using functionalized ethoxyvinyl esters **3** and the Diels–Alder reaction of the intermediates (*R*)-**4**. The finding that the ruthenium catalysts (**1f** and **1g**) produced a fast racemization of the slow-reacting enantiomers (*S*)-**2** with reduced formation of the side products **6** was the key to the success of this process, and the products **5**, useful chiral intermediates for natural products such as compactin[10] and forskolin,[11] were directly obtained with up to 95% *ee* in 81% yield (Scheme 1).

Three separate reactions, that is, the enantioselective KR of (±)-**2**, the racemization of the slow-reacting enantiomer, and the Diels–Alder reaction of **4** have to proceed under identical conditions to achieve the domino reaction with DKR.

The lipases and organic solvents were first screened in the standard KR of (±)-**2a** with the ethoxyvinyl maleate **3a**,[12] and we found that the use of *Candida antarctica* lipase,



Scheme 1. Preparation of **5** by a lipase-catalyzed domino DKR/Diels–Alder reaction. MS = molecular sieves.

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fraction B (CALB, commercially available from Roche Diagnostics) in toluene caused the domino reaction to give **5a** ($R^1 = H$, $R^2 = Et$), although the enantioselectivity and the yield were poor (entry 1 in Table 1). On the other hand, the more polar solvents such as CH_2Cl_2, acetone, and MeCN were quite efficient for both the enzymatic resolution and the subsequent Diels–Alder reaction of **4a** ($R^1 = H$, $R^2 = Et$). After two days at 30 °C, **5a** (93–95 % *ee*, 35–43 % yield) was isolated, along with (*R*)-**4a** and (*S*)-**2a** (entries 2–4).[13,14] Prolonging the reaction time to five days completed the Diels–Alder reaction, and **5a** (90–93 % *ee*, 44–47 % yield) and (*S*)-**2a** (99 % *ee*, 46–50 % yield) were obtained (entries 5–7). Similar reactions at 40 °C, however, resulted in a slightly lower enantioselectivity (87–91 % *ee*), and therefore a reaction temperature lower than 40 °C was recommended.

The next and most critical subject in this study was the development of a highly effective catalyst for the racemization of (*S*)-**2a** at around 30 °C, because **1a–e** were not always effective for the lipase-catalyzed DKR at ambient temperature and often generated considerable amounts of ketones that caused a decrease in the yields of the desired products.[2–6]

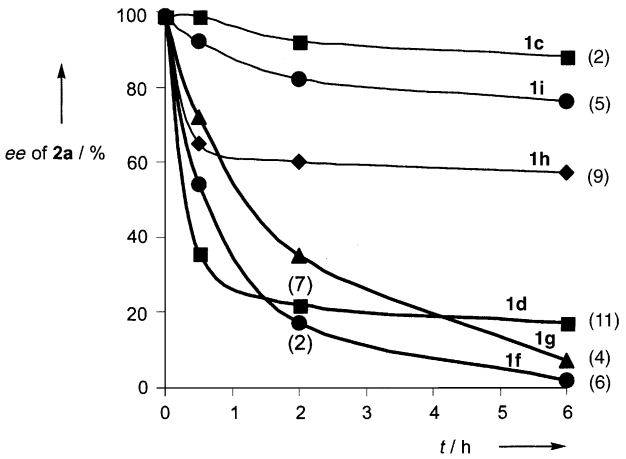


Figure 1. Time-course plot of the racemization of (*S*)-**2a** (99 % *ee*; 0.04 M) and the yield (%) of **6a** (shown in the parentheses) in CH_2Cl_2 with a ruthenium catalyst (**1c** (■), **1d** (■), **1f** (●), **1g** (▲), **1h** (◆), and **1i** (●)) at 25 °C. The combination of a ruthenium catalyst and a base (**1c** with *t*BuOK (8 and 10 mol %, respectively) or **1d**, **1f–i** and Et_3N (4 mol % and 1 equiv, respectively)) was used.

Table 1: Lipase-catalyzed KR of (±)-**2a** using **3a**.[a]

Entry	Solvent	*t* [days]	(*R*)-**4a**[a]		**5a**[b]		(*S*)-**2a**[b]	
			ee [%][b]	yield [%][c]	*ee* [%][b]	yield [%][c]	*ee* [%][b]	yield [%][c]
1	toluene	2	11	43	31	25	91	17
2	CH_2Cl_2	2	69	10	93	38	98	48
3	acetone	2	77	12	95	35	99	49
4	MeCN	2	91	7	93	43	99	44
5	CH_2Cl_2	5	trace	92	44	99	50	
6	acetone	5	trace	90	45	99	50	
7	MeCN	5	trace	93	47	99	46	

[a] A mixture of (±)-**2a** (0.12 mmol), **3a** (0.18 mmol), CALB (15 mg), and molecular sieves (3 Å; 60 mg) was stirred in a solvent (1.0 mL) at 30 °C. [b] For determination of the optical purity and the absolute stereochemistry, see ref. [14] and the Supporting Information, respectively. [c] Yields are based on ^{1}H NMR analysis.

Thus, the racemization of (*S*)-**2a** (99 % *ee*) with **1c** in CH_2Cl_2 at 25 °C was slow,[15] and that with **1d** provided an 11 % yield of the ketone **6a** after 6 h (Figure 1).

We found $[\{RuCl_2(mesitylene)\}_2]$ (**1f**) and $[\{RuCl_2(C_6Me_6)\}_2]$ (**1g**), which were readily available by the reported methods and stable at room temperature[16] but had not previously been used as catalysts for the racemization of optically active secondary alcohols, were more effective, and the reaction with these catalysts featured a higher reactivity and decreased formation of **6a**. On the other hand, the related catalysts $[\{RuCl_2(benzene)\}_2]$ (**1h**) and $[\{RuCl_2(anisole)\}_2]$ (**1i**) were not reactive (Figure 1). A further comparison of **1d**, **1f**, and **1g** for the racemization of (*S*)-**2a** in acetone disclosed that **1d** generated **6a** in 37 % yield with complete racemization, whereas **1f** and **1g** depressed the formation of **6a** to less than 10 % yield. A similar tendency was observed in MeCN (see the Supporting Information for further details).[17]

With these preliminary results in hand, we examined the domino DKR process with **1f** in CH_2Cl_2, acetone, or MeCN. Thus, a mixture of (±)-**2a**, **3a** (3 equiv), CALB, **1f** (4–10 mol %), Et_3N (3 equiv), and molecular sieves (3 Å) was stirred in the solvent at 35 °C. Although the reaction with 4 mol % of **1f** proceeded slowly because of the insufficient rate of racemization compared to the lipase-catalyzed KR, the use of 10 mol % of **1f** was found to be effective (Scheme 1). The reaction in acetone gave **5a** (95 % *ee*, 86 % yield as measured by ^{1}H NMR spectroscopy, 81 % yield after isolation) along with **6a** (9 % yield as measured by ^{1}H NMR spectroscopy; entry 2 in Table 2), and that in MeCN produced a similarly good result (**5a** with 97 % *ee* in 81 % yield as measured by ^{1}H NMR spectroscopy; entry 3). Compound **5a** was obtained with a lower optical purity in CH_2Cl_2 in an unsatisfactory yield as a result of the greater formation of **6a** (22 % yield; entry 1).

Under conditions similar to those listed in entry 2 in Table 2, the racemic alcohols **2a–c** and the acylating reagents (**3a**,**b**)[12] were subjected to the domino reaction, and the corresponding cycloadducts **5b–d** were isolated in good to high yields with more than 90 % *ee* (entries 4–6). This new procedure has the following advantages compared with the previous stepwise preparation of **5** from **2**: 1) the preparation of optically active **5a** and **5b** (entries 2 and 4) proceeds in higher yields than the previous preparation of the corresponding racemates (**5a**[10] and **5b**[13a] in 39 % and 67 % overall yields, respectively), and 2) the efficiency of our enzymatic resolution of (±)-**2c** (entry 6) is higher than that of the standard enzymatic KR of the same substrate.[18]

In addition, the one-pot synthesis was achieved from the preparation of **3b** from monomethyl maleate **7b** followed by the domino DKR process with (±)-**2a**. Catalyst **1d** was used for the first step because **1f** did not effectively accelerate the

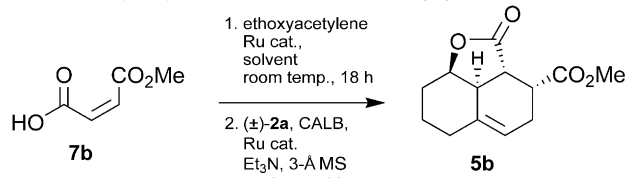
Table 2: Lipase-catalyzed domino DKR/Diels–Alder reaction of (±)-**2a–c** with **3a,b** to give **5**.[a]

Entry	(±)-**2**	**3**	Reaction conditions	**5**				**6** (Yield [%])[c]
				R^1	R^2	*ee* [%][b]	yield [%]	
1	(±)-**2a**	**3a**	CH_2Cl_2, 35 °C, 3 days	H	Et	**5a**: 82	73[c]	**6a** (22)
2	(±)-**2a**	**3a**	acetone, 35 °C, 3 days	H	Et	**5a**: 95	86[c] (81[d,e])	**6a** (9)
3	(±)-**2a**	**3a**	MeCN, 35 °C, 3 days	H	Et	**5a**: 97	81[c]	**6a** (13)
4	(±)-**2a**	**3b**	acetone, 35 °C, 3 days	H	Me	**5b**: 93	83[d,e]	**6a** (6)
5	(±)-**2b**	**3b**	acetone, 25 °C, 4 days	Me	Me	**5c**: 91	81[d,f]	**6b** (4)
6	(±)-**2c**	**3a**	acetone, 25 °C, 7.5 days	$S(CH_2)_3S$	Et	**5d**: 93	69[d,f,g]	**6c** (2)

[a] Typical procedure: A mixture of (±)-**2** (0.49 mmol), **3** (1.5 mmol), CALB (60 mg), **1f** (0.049 mmol), Et_3N (1.5 mmol), and molecular sieves (3 Å; 240 mg) was stirred in solvent (5 mL) in an argon atmosphere and the stated conditions. [b] For determination of the optical purity and the absolute stereochemistry, see ref. [14] and the Supporting Information, respectively. [c] Yield determined by ^{1}H NMR analysis. [d] Yield after isolation of the product. [e] A minor product (approximately 3–4% based on 500 MHz ^{1}H NMR analysis) that seemed to be a diastereomer was present as a contaminant after standard SiO_2 chromatography. [f] Obtained as a single diastereomer (500 MHz ^{1}H NMR analysis) after standard SiO_2 chromatography. [g] The diastereomer was obtained separately (approximately 8% yield) as well as **5d**.

addition of **7b** to ethoxyacetylene, and then (±)-**2a** and the reagents for the domino DKR reaction were added directly to give **5b** (94% *ee*, 81% yield; entry 1 in Table 3; see the Experimental Section for further details).[14] Another procedure involving **1g** for both steps also afforded **5b** (90% *ee*, 80% yield; entry 2 in Table 3). Although one disadvantage of these one-pot procedures is the long reaction time, we could obtain a potential strategy for a high-atom-economy process.

Table 3: One-pot synthesis of **5b** from **7b** and (±)-**2a**.



Entry	Ru cat./solvent for the first step	Ru cat./solvent for the second step	**5b**	
			ee value [%]	yield [%][a]
1	**1d** (0.5 mol%)/ acetone	**1f** (10 mol%)/ MeCN	94	81
2	**1g** (1 mol%)/ MeCN	**1g** (10 mol%)/ MeCN	90	80

[a] A minor product (≦3% based on 500 MHz ^{1}H NMR analysis) that seemed to be a diastereomer was present as a contaminant.

In conclusion, we have demonstrated here the first example of the combination of the domino reaction concept[8,9] and the DKR protocol,[2] a combination which is highly advantageous in terms of a simple and safe procedure, high chemical and optical yields at around room temperature, and the reduction of waste. From a mechanistic point of view, the successful use of acetone for the DKRs is extraordinary, because acetone acts as a hydrogen acceptor and thereby has been believed to accelerate the formation of the undesired ketones.[4a] Extensive study of other systems and the mechanistic elucidation are now in progress in our laboratory.

Experimental Section

3a: A mixture of ethoxyacetylene (1.88 mL, 23 mmol) and **1d** (92 mg, 0.15 mmol) in anhydrous acetone (50 mL) was stirred at 0 °C for 5 min under a nitrogen atmosphere, and a solution of monoethyl maleate **7a** (2.2 g, 15 mmol) in anhydrous acetone (20 mL) was added dropwise over 20 min. The reaction mixture was stirred at room temperature for 18 h and concentrated in vacuo to give **3a** (approximately 90% pure based on ^{1}H NMR analysis). Pure **3a** (1.59 g, 50% yield) was obtained by distillation as a colorless oil: b.p. 120–130 °C/0.4 Torr (bath temperature); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$–1.41 (6H, m), 3.82 (1H, d, $J = 4.5$ Hz), 3.89 (2H, q, $J = 8$ Hz), 3.96 (1H, d, $J = 4.5$ Hz), 4.27 (2H, q, $J = 8$ Hz), 6.26 (1H, d, $J = 13$ Hz), 6.35 ppm (1H, d, $J = 13$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$, 14.1, 61.5, 65.0, 72.2, 127.7, 132.0, 156.6, 162.1, 164.9 ppm; IR (KBr): $\tilde{\nu} = 1759$, 1732, 1678 cm^{-1}; elemental analysis: calcd: C 56.07, H 6.59; found: C 55.79, H 6.54.

3b: b.p. 108–110 °C/1.5 Torr (bath temperature).

One-pot preparation of **5b** from **7b** and (±)-**2a** (entry 1 in Table 3): Similarly to the preparation of **3a**, a mixture of ethoxyacetylene (0.26 mL, 3.1 mmol), **7b** (0.27 g, 2.1 mmol), and **1d** (6.4 mg, 0.010 mmol) in anhydrous acetone (6 mL) was stirred at room temperature for 18 h and concentrated in vacuo. (±)-**2a** (60 mg, 0.49 mmol), **1f** (29 mg, 0.049 mmol), powdered molecular sieves (3 Å; predried at 140 °C, 1 Torr for 2 h, 120 mg), and CALB (60 mg) were successively added to this mixture. The flask was evacuated (approximately 20 Torr) at room temperature for 10 s and flushed with argon. Anhydrous MeCN (4 mL) and Et_3N (0.20 mL, 1.45 mmol) were added under an argon atmosphere, and the flask was sealed. The reaction mixture was stirred at 35 °C for 4.5 days and filtered through a celite pad. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on SiO_2 (hexanes/EtOAc, (5:1→2:1)) to give **5b** (92 mg, 81% yield) as white crystals. A minor product (≦3% based on 500 MHz ^{1}H NMR analysis) was also present that seemed to be a diastereomer. The optical purity of this product was determined to be 94% *ee* by HPLC with a Daicel Chiralcel OD chiral column (hexanes/*i*PrOH (90:10), flow rate = 1.0 mL min^{-1}). M.p. 73–74 °C; $[\alpha]_D^{27} = -32$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR, ^{13}C NMR, and IR spectroscopic data were in good agreement with the reported value of the racemate;[13a] elemental analysis: calcd: C 66.09, H 6.83; found: C 65.88, H 6.88.

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Keywords: asymmetric synthesis · cycloaddition · domino reactions · kinetic resolution · lipases

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[12] Novel acylating reagents (**3a**,**b**) were prepared by the addition of the monoalkyl maleate **7** to ethoxyacetylene in a similar way to the preparation of the related ethoxyvinyl esters.[9b] Although initial studies were carried out with purified **3** to examine diverse reaction conditions, a more practical one-pot method with crude **3** also gave a similar result, as shown in Table 3.
[13] The related intramolecular Diels–Alder reactions have been carried out at high temperatures, such as 120–150 °C, in aromatic solvents or with microwave irradiation; however, the yields of the products were moderate.[10,13a] We found that the reaction of **4a** in polar solvents gradually proceeded even at room temperature to give almost quantitative yields of **5a**. a) M. J. Batchelor, J. M. Mellor, *J. Chem. Soc. Perkin Trans. 1* **1989**, 985 – 995; for a similar example, see: b) P. Magnus, C. Walker, *Tetrahedron Lett.* **1986**, *27*, 651 – 654.
[14] Optically purity of the products was determined by HPLC analysis with a chiral column: Daicel Chiralcel OD for **2a**, **4a**, **5a**, and **5b**, Daicel Chiralpak AD-H for **5c** and **5d**. The absolute and relative stereochemistries of the products were determined as shown in the schemes (see the Supporting Information for further details).
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