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Chemoenzymatic Dynamic Kinetic Resolution of Axially Chiral Allenes

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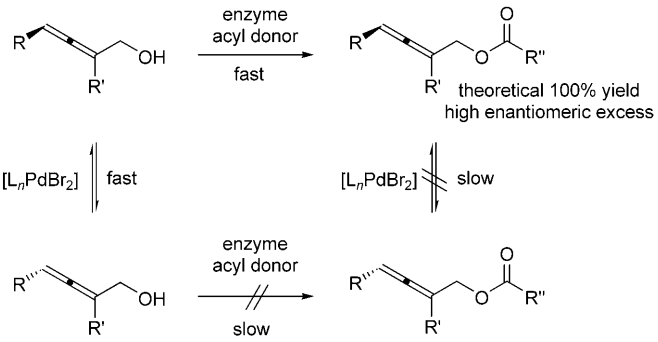
Dedicated to Professor Uli Kazmaier on the occasion of his 50th birthday

Although racemization is normally an undesired reaction in asymmetric synthesis, its combination with a resolution process is a powerful approach for obtaining enantiomerically pure compounds. Resolution of racemic mixtures[1] by physical or chemical means, and particularly by enzyme catalysis,[2] is still often the method of choice when it comes to the production of optically pure material. However, kinetic resolution of racemates suffers from the limitation of a maximum theoretical yield of 50% for one pure enantiomer. The undesired enantiomer remains as waste and has to be removed from the product in an additional purification step. At this point, controllable and selective racemization protocols come into play as they allow for in situ interconversion of the slow reacting enantiomer into its mirror image (and vice versa) leading to dynamic kinetic resolution (DKR), where 100% yield together with high enantiomeric purity becomes possible.

Based on this strategy, a plethora of novel approaches has arisen over the past decade, combining various different racemization processes with chemical[3] or enzymatic[4] resolution making DKR a versatile and powerful tool in asymmetric synthesis. Although DKR procedures are well known for centrochiral compounds, dynamic kinetic approaches dealing with axially, planar or helically chiral substrates are extremely rare.[5,6] Allenes are an important class of axially chiral compounds[7] and in the present study we report on a novel chemoenzymatic DKR of allenes, in which an NHC–palladium complex is employed as racemization catalyst.

In the field of dynamic kinetic resolution, our group is particularly interested in the combination of transition metal mediated racemization processes with enzymatic resolution.[8] Recently, we reported the use of porcine pancreatic lipase (PPL) as a highly efficient biocatalyst for the kinetic resolution of axially chiral primary allenic alcohols with excellent enantioselectivities.[9] With this tool in hand, the strategy was to develop a DKR by combining the enzymatic transesterification[10] with a Pd-catalyzed allene racemization previously developed in our laboratory (Scheme 1).[11] In



Scheme 1. Principle of a chemoenzymatic allene DKR.

contrast to other DKR approaches, the chiral group that is racemized in the starting material is also present in the product. To avoid undesired product racemization, catalytic systems with a substantial selectivity for the starting material are required, that is, a faster racemization of the chiral allene moiety in the allenol compared to the allenyl ester.

Unfortunately, the reported[11] catalysts, [Pd(OAc)$_2$]/LiBr and [(PhCN)$_2$PdBr$_2$]), racemized the allenol and the product allenyl ester with about the same rate (vide infra). Furthermore, these catalysts were incompatible with the enzyme PPL, leading to a dramatically reduced biocatalytic activity. Nevertheless, by combining PPL-catalyzed kinetic resolution of allenol **1a** with the [Pd(OAc)$_2$]/LiBr-catalyzed racemization in a sequential fashion, optically active butyrate (*R*)-**2a** was obtained in high enantiomeric excess and 71% isolated yield after only one recycling (Scheme 2). Thus, after a first kinetic resolution, the remaining enantioenriched alcohol (*S*)-**1a** was isolated, racemized, and subjected to a second enzymatic cycle.

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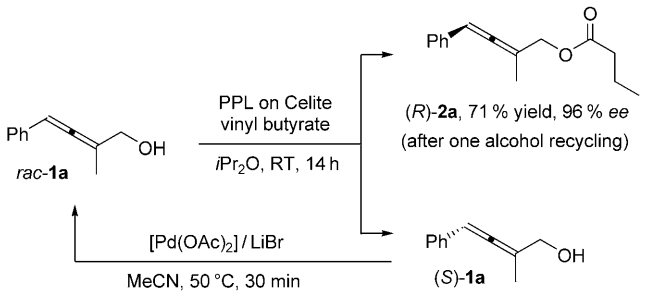
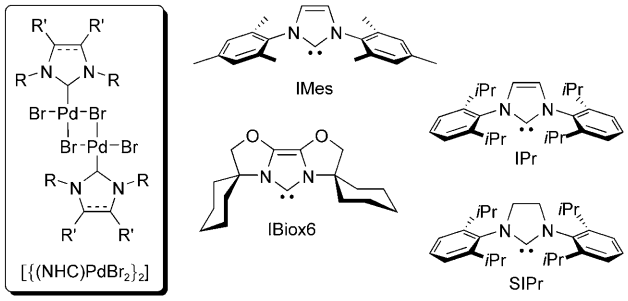


Scheme 2. Sequential kinetic resolution/racemization.



Scheme 3. NHC–palladium complexes used in allene racemization.

For a one-pot dynamic kinetic resolution, novel racemization catalysts are required that are compatible with the biocatalyst and racemize the substrate faster than the product. Therefore, a screening of potential catalysts for the allene racemization was performed, studying the progressive loss of enantiopurity over time of (*S*)-**1a** and (*R*)-**2a**. Both [Pd(OAc)$_2$]/LiBr and [(MeCN)$_2$PdBr$_2$] (5 mol%) gave fast racemization of alcohol (*S*)-**1a** and butyrate (*R*)-**2a** at 50°C with only a marginally longer half time of the latter. As mentioned above these catalysts are not compatible with PPL and were therefore not applicable in a DKR process (Table 1, entries 1 and 2). With stronger binding ligands, such as triphenylphosphine, pyridine, or 2,2′-bipyridine, virtually no racemization was detected (Table 1, entries 3–5). These observations suggest that efficient racemization requires at least one labile ligand to open up a coordination site for the allene. Furthermore, we argued that sterically demanding ligands on Pd would minimize undesired metal–protein interaction. Large ligands might also favor racemization of the allenol over the allenyl butyrate. In search of suitable catalysts complying with these demands, the class of dimeric *N*-heterocyclic carbene palladium complexes attracted our attention (Scheme 3).

Table 1. Palladium-catalyzed racemization of allenol (*S*)-**1a** and butyrate (*R*)-**2a**.[a]

Entry	Pd source	$t_{1/2}$ (**1a**) [h][b]	$t_{1/2}$ (**2a**) [h][b]	Selectivity[c]
1[d]	[Pd(OAc)$_2$]/LiBr	0.12	0.13	1.1
2	[(MeCN)$_2$PdBr$_2$]	0.27	0.43	1.6
3	[(PPh$_3$)$_2$PdBr$_2$]		no racemization	
4	[(Py)$_2$PdBr$_2$]		no racemization	
5	[(Bipy)PdBr$_2$]		no racemization	
6	[{(IMes)PdBr$_2$}$_2$]	12	67	5.4
7	[{(IPr)PdBr$_2$}$_2$]	13	69	5.3
8	[{(SIPr)PdBr$_2$}$_2$]	31	141	4.5
9	[{(IBiox6)PdBr$_2$}$_2$]	70	74	1.1

[a] Reactions performed at 50°C with (*S*)-**1a** (50 μmol) or (*R*)-**2a** (50 μmol) and Pd catalyst; entries 1–5: 2.5 μmol (5 mol%); entries 6–9: 0.5 μmol (1 mol%) in toluene (1 mL). [b] Determined by chiral HPLC. [c] Selectivity = $t_{1/2}$(**2a**):$t_{1/2}$(**1a**). [d] MeCN was used as solvent.

The NHC–Pd complexes offer one bulky, strictly nondissociating ligand along with a relatively labile bridging bromide[12] that is readily displaced by the cumulated diene. Further advantages of these complexes are tolerance towards air and easy accessibility from the parent carbene and an appropriate palladium source.[12c] To our delight racemization occurred smoothly at 50°C with 1 mol% of [{(IMes)PdBr$_2$}$_2$] or [{(IPr)PdBr$_2$}$_2$] and, importantly, with about a fivefold preference for allenic alcohol **1a** over butyrate **2a** (Table 1, entries 6 and 7). Saturated NHC complex, [{(SIPr)PdBr$_2$}$_2$] showed good selectivity and enzyme compatibility, but the catalyst suffered from lower activity as indicated by extended half times of racemization (Table 1, entry 8). The bioxazoline-derived complex [{(IBiox6)PdBr$_2$}$_2$], however, did not show any selectivity in racemization of alcohol **1a** versus butyrate **2a** (Table 1, entry 9).

With these selective racemization catalysts in hand, the question arose whether the bulky NHC ligands would also be able to diminish the undesirable enzyme inhibition and thereby facilitate an integrated chemoenzymatic DKR process. Hence, we conducted PPL-catalyzed kinetic resolution of **1a** in the presence of different concentrations of palladium bromide and studied the relative activities of the biocatalyst at 35°C. Gratifyingly, none of the NHC–Pd dimers caused the severe enzyme poisoning observed with other palladium sources. As illustrated for [{(IPr)PdBr$_2$}$_2$] (Figure 1) good activity of PPL was maintained even at high

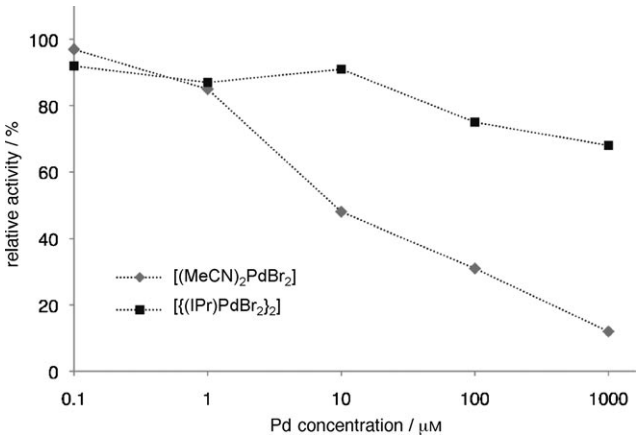
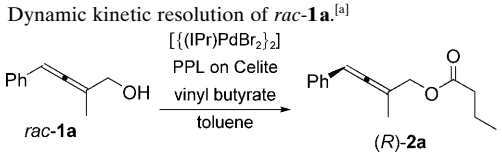


Figure 1. Relative activity of PPL in the presence of [(MeCN)$_2$PdBr$_2$] and [{(IPr)PdBr$_2$}$_2$]. Reaction conditions: *rac*-**1a** (50 μmol), vinyl butyrate (250 μmol), PPL (20% on Celite 500, 7.5 mg) in toluene (1 mL) at 35°C for 8 h; conversion and *ee* determined by chiral HPLC.

metal concentrations (up to 1 mM). In contrast, by using $[(MeCN)_2PdBr_2]$ a significant drop in activity of about 50% was already observed at 10 μM and almost complete inhibition took place at 1 mM (Figure 1). In the same experiments, the impact of the NHC–Pd species on the enzyme's enantioselectivity was analyzed. Just as for the activity, also the selectivity was only marginally affected by the presence of $[\{(IPr)PdBr_2\}_2]$. The *E* value for the kinetic resolution of *rac*-**1a** decreased from 270 under palladium-free conditions to 200 in a 0.5 mM $[\{(IPr)PdBr_2\}_2]$ solution.[13]

Taking into account different properties, such as racemization rates, substrate selectivity, protein tolerance and solubility, $[\{(IPr)PdBr_2\}_2]$ was chosen as the racemization catalyst for further studies of an integrated DKR process (Table 2).

Table 2. Dynamic kinetic resolution of *rac*-**1a**.[a]



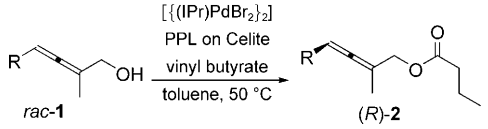
Entry	Enzyme[b] [mg mmol^{-1}]	Pd catalyst [mol%]	T [°C]	Time [h]	Yield [%]	*ee*[c] [%]
1	15	1	40	32	47	96
2	15	1	50	30	72	89
3	15	1	60	24	69	83
4[d]	15+15	1	50	30	76	84
5	30	1	50	30	77	78
6	30	2	50	23	81	86

[a] Reactions performed with *rac*-**1** (100 μmol), vinyl butyrate (500 μmol), $[\{(IPr)PdBr_2\}_2]$ (1–2 μmol) and porcine pancreatic lipase (20 wt% on Celite 500) in toluene (2 mL); [b] weight specification refers to the amount of protein excluding solid support; [c] *ee* determined by chiral HPLC; [d] PPL was added in two steps, 15 mg mmol^{-1} at the beginning of the reaction and 15 mg mmol^{-1} after 10 h.

PPL shows its optimal performance below 50 °C. At an elevated temperature, a decrease in selectivity and activity was observed.[14] To reduce these effects, immobilized PPL was used in the DKR studies, with Celite as solid support.[15] On the other hand, the racemization catalyzed by $[\{(IPr)PdBr_2\}_2]$ could not reach sufficient rate below 50 °C without prohibitive increase of catalyst loading. Therefore, at 40 °C despite the presence of the dimeric Pd complex, only ordinary kinetic resolution was obtained (Table 2, entry 1). By increasing the reaction temperature, a dynamic behavior was achieved and the best results were observed at 50 °C (Table 2, entry 2). At 60 °C, probably as a consequence of thermal deactivation[16] of the enzyme in combination with faster product racemization, yield and enantiopurity of (*R*)-**2a** decreased (Table 2, entry 3). Attempts to counteract thermal protein deactivation by increasing the enzyme loading, both in a single addition (Table 2, entry 4) or in a stepwise manner (Table 2, entry 5) led to a slight improvement in yield, but at the expense of enantioselectivitiy due to over-acylation. However, with double amounts of both enzyme and palladium catalyst, a successful DKR was achieved combining good yield (81%) with high enantiomerical purity (e.r. = 93:7; Table 2, entry 6). These results reflect the delicate balance between required catalyst activity and undesired product racemization, and reveal the necessity for the further development of more selective racemization catalysts. Nonetheless, regarding the important task of this novel DKR approach, the results obtained with this relatively simple and readily available catalytic system can be considered as more than satisfying.

Next, the transferability of this first chemoenzymatic dynamic kinetic resolution of axially chiral molecules to related substrates was investigated. Thereby, different substituted allenic alcohols were treated under optimized conditions. All aryl substituted butyrates (**2a**–**2d**) could be isolated in similarly high enantiomeric excess >85% and in good yield (Table 3, entries 1–4). The lower conversion obtained for the *meta*-tolyl derivative (*R*)-**2b** can be explained by the lower reactivity of the parent alcohol, as already observed in the ordinary kinetic resolution.[9]

Table 3. Influence of substituents in allene DKR.[a]



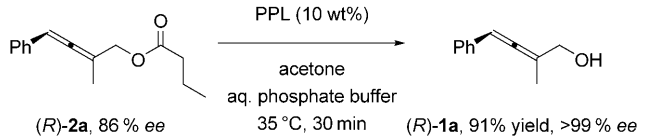
Entry	Alcohol	R	Time [h]	Yield [%]	*ee*[b] [%]
1	**1a**	phenyl	23	**2a**: 81	86
2	**1b**	3-tolyl	27	**2b**: 70	89
3	**1c**	2-naphthyl	24	**2c**: 83	89
4	**1d**	4-chlorophenyl	21	**2d**: 80	87
5	**1e**	*n*-pentyl	20	**2e**: 87	66

[a] Reactions performed at 50 °C with allenic alcohol (100 μmol), vinyl butyrate (500 μmol), $[\{(IPr)PdBr_2\}_2]$ (2 μmol) and PPL (20 wt% on Celite 500, 15 mg) in toluene (2 mL); [b] *ee* determined by chiral HPLC.

Only the aliphatic allenyl butyrate (*R*)-**2e** did not reach the same degree in optical purity (Table 3, entry 5). A reason for this is the significantly lower enantioselectivity of the biocatalyst for this kind of substrate.[9]

An exceptional feature of lipases is their ability to catalyze reactions in aqueous media as well as in highly unpolar organic solvents. The same enzyme used to conduct a kinetic resolution by means of stereoselective esterification of alcohols under nonaqueous conditions is also capable of mediating stereoselective ester hydrolysis when water is used as solvent. In case of allene DKR, subsequent enzymatic hydrolysis of the enantioenriched esters was exploited as a second stereoselection step, allowing for further enhancement of optical purity. Thus, treatment of butyrate (*R*)-**2a** (86% *ee*) with catalytic amounts of crude PPL in neutral phosphate buffer and acetone as cosolvent led to fast hydrolysis and after 30 min enantiopure alcohol (*R*)-**1a** was isolated in 91% yield (Scheme 4).[17]

In conclusion, we have developed a novel method in the field of coupled bio- and transition metal catalysis, allowing



Scheme 4. Enantioenrichment by enzymatic deprotection.

for the first time the chemoenzymatic dynamic kinetic resolution of axially chiral allenes. Thus, the combination of an NHC–palladium catalyst together with porcine pancreatic lipase provides allenyl butyrates in good to high yields and in *ee* values up to 89%. Detailed studies regarding the racemization mechanism of these palladium catalysts are presently being investigated in our laboratories.

Experimental Section

Synthesis of [{(IPr)PdBr$_2$}$_2$]:[12c] A solution of 1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene (198 mg, 0.51 mmol) in dry THF (3 mL) was added dropwise to a suspension of [(MeCN)$_2$PdBr$_2$] (174 mg, 0.50 mmol) in dry THF (2 mL) and dry toluene (3 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 3 h resulting in a deep red solution. After filtration through Celite and washing with THF, the filtrate was concentrated and subjected to flash chromatography (SiO$_2$, pentane/Et$_2$O/CH$_2$Cl$_2$, 10:1:1) yielding an orange powder (224 mg, 0.171 mmol, 68% yield). Crystallization was performed by slow evaporation from chloroform in an open flask; m.p. 264–267°C (decomp.); ^{1}H NMR (400 MHz, CDCl$_3$): δ [ppm] = 0.92 (d, J = 7.0 Hz, 12H), 1.03 (d, J = 7.0 Hz, 12H), 1.21 (d, J = 7.0 Hz, 12H), 1.39 (d, J = 7.0 Hz, 12H), 2.64 (hept, J = 7.0 Hz, 4H), 3.03 (hept, J = 7.0 Hz, 4H), 6.99 (s, 4H), 7.24 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 8.0 Hz, 4H), 7.52 (t, J = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ [ppm] = 23.4, 26.4, 28.8, 124.2, 124.4, 125.5, 130.3, 134.6, 146.1, 146.6, 153.0; HRMS (ESI): calcd for $C_{54}H_{72}Br_4N_4NaPd_2$ [M+Na]$^+$: 1333.0439, found 1333.0436.

Dynamic kinetic resolution: *rac*-**1a** (32.0 mg, 200 μmol) and [{(IPr)PdBr$_2$}$_2$] (5.2 mg, 4 μmol) were dissolved in toluene (4 mL). Porcine pancreatic lipase (30 mg, 20 wt% on Celite 500) and vinyl butyrate (126 μL, 1.0 mmol) were added and the mixture was stirred at 50°C for 23 h. After filtration through silica and concentration of the filtrate in vacuo, the residual oil was purified by column chromatography (SiO$_2$, pentane/Et$_2$O, 93:7) yielding (*R*)-**2a** as a colorless oil (37.2 mg, 162 μmol, 81%, 86% *ee*). $[\alpha]_D^{20} = -8.6°$ (*c* 0.7, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ [ppm] = 0.90 (t, J = 7.4 Hz, 3H), 1.61 (tq, J = 7.4 Hz, 2H), 1.83 (d, J = 2.8 Hz, 3H), 2.28 (t, J = 7.3 Hz, 2H), 4.58–4.67 (m, 2H), 6.17 (tq, J = 2.8 Hz, 1H), 7.18–7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ [ppm] = 13.6, 15.9, 18.4, 36.1, 64.8, 95.7, 99.9, 126.9, 127.0, 128.5, 134.4, 173.3, 203.2; HRMS (ESI): calcd for $C_{15}H_{18}NaO_2$ [M+Na]$^+$: 253.1199, found: 253.1199; HPLC (Chiralcel OB, isohexane/*i*PrOH, 92:8, 0.5 mL min^{-1}, 249 nm): $t_R(R)$ = 12.1 min, $t_R(S)$ = 18.5 min.

Enzymatic hydrolysis: (*R*)-**2a** (34.5 mg, 150 μmol, 86% *ee*) was dissolved in acetone (0.5 mL) and aqueous phosphate buffer (1 mL, pH 7.4). The solution was warmed to 35°C, crude PPL (3.5 mg) was added and the mixture was stirred for 30 min at 35°C. After filtration through a plug of Celite, the filtrate was extracted three times with Et$_2$O, the combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Column chromatography (SiO$_2$, pentane/Et$_2$O, 7:3) yielded (*R*)-**1a** (21.8 mg, 136 μmol, 91%, >99% *ee*) as colorless needles; m.p. 89°C; $[\alpha]_D^{20} = -10.9°$ (*c* 0.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ [ppm] = 1.69 (bs, 1H), 1.84 (d, J = 2.9 Hz, 3H), 4.10–4.18 (m, 2H), 6.28 (tq, J = 3.0 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ [ppm] = 15.4, 63.8, 97.0, 106.7, 126.8, 127.0, 128.6, 134.7, 200.8; HRMS (ESI) calcd for $C_{11}H_{12}NaO$ [M+Na]$^+$: 183.0785, found: 183.0780; HPLC (Chiralcel OB, isohexane/*i*PrOH, 92:8, 0.5 mL min^{-1}, 249 nm): $t_R(R)$ = 14.2 min, $t_R(S)$ = 15.7 min.

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Keywords: allenes · biocatalysis · dynamic kinetic resolution · palladium · racemization

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