DOI: 10.1002/ejoc.200901025

Dynamic Enzymatic Kinetic Resolution of Methyl 2,3-Dihydro-1*H*-indene-1-carboxylate

Jörg Pietruszka,*[a] Robert Christian Simon,[a] Fabian Kruska,[b] and Manfred Braun[b]

Keywords: Hydrolases / Enzyme catalysis / Racemisation / Kinetic resolution / Domino reactions

A new reaction setup for kinetic enzymatic resolution was established and is demonstrated for the case of the hydrolase-catalysed conversion of methyl 2,3-dihydro-1*H*-indene-1-carboxylate (**1**) in conjunction with a base-catalysed racemisation. The system allows controlled racemisation, resulting in efficient dynamic kinetic resolution (DKR) of the title compound. Short reaction times and high enantioselectivities were obtained with CAL-B and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene). Compound (*R*)-**1** (*ee* 95 %) served as a starting material in a domino reaction that led to the biaryl indanyl ketone (*R*)-**8**, a lead compound for novel inhibitors of peptidyl-prolyl-*cis*/*trans*-isomerases, in 94 % *ee*.

Introduction

Enzymatic kinetic resolution is a powerful method for the separation of enantiomers of a racemate, obviously due to the high stereo- and regioselectivities of these biocatalysts. However, the major drawback is the limitation of a 50 % theoretical yield of the desired enantiomer when starting with racemic material. To overcome this disadvantage, the undesired enantiomer may in some cases be isolated, subjected to racemisation and resubjected to the resolution procedure; as a consequence, quantitative conversion of a racemic substrate into a single desired enantiomer is feasible. Dynamic resolution, in which the kinetic resolution process is coupled with a continuous in situ racemisation of the starting material, has become very popular, with a variety of different methods having been established during recent years.[1,2] Common enzymatic kinetic resolutions have been combined with different racemisation techniques variously utilizing transition metals,[3–5] bases and acids[6,7] or ion-exchange resins.[8,9] Different strategies to combine these two steps have been developed; in principle the reactions are performed in one vessel, but a two-compartment system has also been established by Bornscheuer and coworkers.[8] The aim of our endeavour was to obtain access to both enantiomers of indane-1*H*-carboxylic acid (**1**) in a convenient manner through a kinetic enzymatic resolution procedure and to scrutinize the suitability of this substrate for dynamic kinetic resolution (DKR). 2,3-Dihydro-1*H*-indene-1-carboxylic acid (**1**) is an important precursor for a series of aryl indan-1-yl ketones that are new lead compounds for human pepidyl-prolyl-*cis*/*trans*-isomerase (Pin1) inhibitors (Figure 1); the potential of the racemic compounds has previously been communicated and here we describe in detail an enantioselective synthesis including a domino coupling.[10]

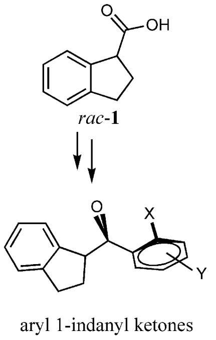

Figure 1. 2,3-Dihydro-1*H*-indene-1-carboxylic acid (**1**) as a precursor for a series of new lead compounds for Pin1 inhibitors.

Racemic acid **1** had already served as the starting material for the syntheses of N4-substituted arylpiperazines that are active as antagonists at postsynaptic 5-HT_{1A} receptors,[11] and affinity for the same receptor was also observed with 1,9-ethano-bridged tetrahydrobenzazepines, which are also accessible from racemic **1**.[12] Furthermore, the acid has been successfully employed as a chiral derivatisation agent in NMR spectroscopy after fluorination in the α position,

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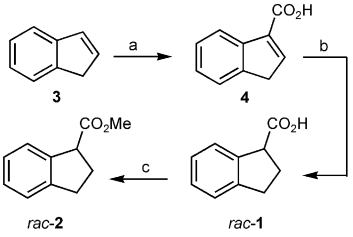
[a] Institut für Bioorganische Chemie der Heinrich Heine Universität Düsseldorf im Forschungszentrum Jülich,
Stetternicher Forst, Geb. 15.8, 52426 Jülich, Germany
Fax: +49-49-2461-616196
E-mail: j.pietruszka@fz-juelich.de
[b] Institut für Organische Chemie und Makromolekulare Chemie, Heinrich Heine Universität Düsseldorf,
Universitätsstraße 1, 40225 Düsseldorf, Germany
E-mail: braunm@uni-duesseldorf.de

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901025.

yielding higher $\Delta\delta_F$ values than the conventional MTPA esters.[13] Despite the simple structure and the common occurrence of the substructure of acid **1**, only a few approaches to enantiopure indane-1*H*-carboxylic acid and its derivatives, utilizing either whole-cell biotransformation[14] or fractional crystallisation,[15,16] had been reported, but either the enantiomeric excess (*ee*) was not satisfactory or the procedures were quite extensive. An efficient DKR procedure would greatly facilitate access to the title compound.

Results and Discussion

Substrate synthesis of methyl 2,3-dihydro-1*H*-indene-1-carboxylate (*rac*-**2**) for subsequent enzymatic kinetic resolution and kinetic studies was straightforward (Scheme 1): indene (**3**) was lithiated with *n*BuLi at low temperature (–78 °C), followed by treatment with solid carbon dioxide (84%). Subsequent hydrogenation of indene-1-carboxylic acid (**4**) under standard conditions (palladium on charcoal) gave the desired acid *rac*-**1** in respectable yield (98%) and short reaction time (12 h). The final esterification with MeOH and sulfuric acid was performed by standard protocols, leading to the required substrate *rac*-**2**. The convenient three-step synthesis was carried out with an overall yield of 76%, starting from indene (**3**).

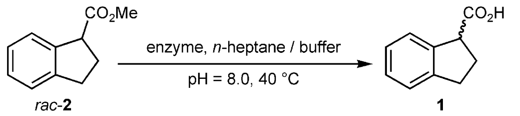


Scheme 1. Synthesis of methyl 2,3-dihydro-1*H*-indene-1-carboxylate (**2**). Reagents and conditions: a) THF, –78 °C, *n*BuLi, 30 min, 0 °C, –78 °C, dry ice, 84%; b) MeOH, room temp., H_2, Pd/C, 98%; c) MeOH, reflux, H_2SO_4, 92%.

Kinetic Resolution

For the enzymatic hydrolysis, 24 different hydrolases[17] were tested on an analytical scale in a biphasic system consisting of a potassium phosphate buffer (100 mM, pH = 8.0, KPi) and *n*-heptane as organic solvent. The reaction mixtures were stirred at 40 °C and after defined intervals small samples were taken to check the enantiomeric excess (*ee*) of substrate **2** by chiral HPLC; a complete analysis (determination of *E* value) was deliberately omitted at the early stage of the investigation. Only a few of the applied enzymes showed good enantioselectivity towards the substrate *rac*-**2** right from the start (Table 1). In our hands, the most promising enzymes were CAL-B (Sigma Aldrich, Entry 6), esterase BS4 (Codexis, Entry 5) and esterase E4 (Boehringer Mannheim, Entry 3), which were used as supplied. Interestingly all of the tested enzymes showed enantiopreference for the *R* enantiomer of substrate **2** with the exception of esterase E4 (Entry 3, Table 1). Nevertheless, because the lipase CAL-B showed the highest conversion and enantioselectivity towards the substrate (*ee* > 99%) in a short period of time, this enzyme was used for a more detailed investigation.

Table 1. Results of the enzyme screening.



Entry	Enzyme	*ee* **2** (3 h)	*ee* **2** (26 h)	Configuration (substrate)
1	esterase E1	> 4%	~ 25%	(*S*)-**2**
2	esterase E3	~ 3%	~ 20%	(*S*)-**2**
3	esterase E4	> 5%	> 90%	(*R*)-**2**
4	PLE	> 8%	> 60%	(*S*)-**2**
5	esterase BS4	> 28%	> 96%	(*S*)-**2**
6	CAL-B	> 99%	> 99%	(*S*)-**2**
7	Amano PS	> 2%	~ 15%	(*S*)-**2**

The results of an enzymatic kinetic resolution may be significantly affected by the organic solvent, as well as by changes in temperature or pH value.[18] Consequently we focused our efforts on the influence of the different parameters, as well as the reaction time, on the *E* values (enantioselectivity).[19] The hydrolysis of ester *rac*-**2** was therefore next performed in the presence of organic solvents as first variable. As predicted,[18b] less polar solvents such as *n*-heptane were superior (Entry 1, Table 2) for the enzymatic kinetic resolution of ester *rac*-**2** because they are not able to remove the outer water shells of the enzymes, which thus maintains their activities and enantioselectivities. The use of toluene or dichloromethane as organic solvent decreased the enantioselectivity to moderate *E* values (*E* = 26 and *E* = 79, respectively), rendering them impractical for further studies.

Table 2. Solvent effects on the hydrolysis of ester *rac*-**2**.

$$rac\text{-}\mathbf{2} \xrightarrow[\text{solvent}]{\text{CAL-B, pH 8.0, 40 °C}} (S)\text{-}\mathbf{2} + (R)\text{-}\mathbf{1}$$

Entry	Solvent	Time (min)	*ee* (*S*)-**2**	*ee* (*R*)-**1**	*E*
1	*n*-heptane	90	> 99%	> 99%	> 100
2	dichloromethane	90	> 97%	> 90%	79
3	MTBE	60	> 94%	> 95%	> 100
4	toluene	60	> 33%	> 90%	26
5	buffer (only)	20	> 94%	> 99%	> 100

We found that the optimum temperature for the hydrolysis of substrate *rac*-**2** was between 40 °C and 50 °C (Table 3); no loss of selectivity either for product (*R*)-**1** or for substrate (*S*)-**2** was observed. At 60 °C the conversion was significantly decelerated, though without any influence on the *ee* of the product (*R*)-**1** (Entry 4). However, these results offer a broad temperature range for the hydrolysis of substrate *rac*-**2** yielding a highly optical pure product (*R*)-**1**.

An alternative synthesis of enantiopure methyl indane-1*H*-carboxylate (**2**) by enzyme-catalysed esterification was elaborated. Through a change in the pH value of the buffer from pH 8.0 to pH 3.4 and addition of methanol, formation of the methyl ester **2** was achieved: the method furnished product (*R*)-**2** in high *ee* (>99%), as shown in Table 4. We

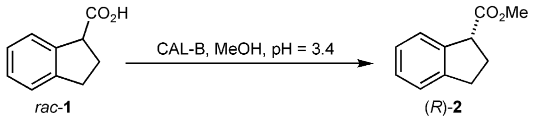
Table 3. Influence of the temperature on the kinetic resolution of *rac*-**2**.

$$rac\text{-}\mathbf{2} \xrightarrow[n\text{-heptane}]{\text{CAL-B, pH 8.0}} (S)\text{-}\mathbf{2} + (R)\text{-}\mathbf{1}$$

Entry	Temp.	*ee* (*S*)-**2**	*ee* (*R*)-**1**	Conv. (%)	*E*
1	30 °C	> 94%	> 95%	50	> 100
2	40 °C	> 98%	> 99%	50	> 100
3	50 °C	> 96%	> 99%	49	> 100
4	60 °C	> 73%	> 99%	42	> 100

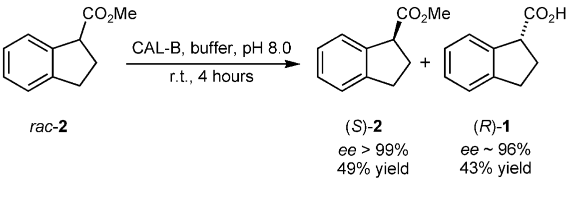
found that the enzymatic esterification proceeded more rapidly in toluene than in *tert*-butyl methyl ether (MTBE); for the hydrolysis we had observed the reverse order. The rate was not very high in the case of MTBE (Entry 3), and the use of *n*-heptane again proved to be most convenient (Entry 1) for forming the *R* enantiomer (as in the hydrolysis) with high enantioselectivity ($E > 100$).

Table 4. CAL-B-promoted enzymatic esterification of *rac*-**1**.



Entry	Solvent	Time	*ee* (*R*)-**2**	*ee* (*S*)-**1**	Conv.	*E*
1	*n*-heptane	70 min	> 99%	93%	48%	> 100
2	toluene	70 min	> 99%	90%	47%	> 100
3	MTBE	70 min	> 99%	28%	22%	> 100

The kinetic resolution of methyl indane-1*H*-carboxylate (*rac*-**2**) was finally performed under optimized conditions on a gram scale (2.0 g, 11.4 mmol): no organic solvent was used, so the reaction temperature could be further decreased to room temperature, and an immobilized form of the *Candida antarctica* lipase B (Novo435)[17] was introduced. Residual ester (*S*)-**2** (49%, $ee > 99\%$) and the formed acid (*R*)-**1** (43%, $ee \approx 96\%$) were obtained with excellent selectivities in high yields at 50% conversion (Scheme 2, Figure 2). It should be pointed out that 2.00 g of the substrate *rac*-**2** were completely resolved within 4 h with the use of just 100 mg of Novo435[17] (CAL-B immobilized, Novo Nordisk). The protein content in Novo435 was determined to be 2% (wt./wt.) of the total mass;[20] hence a real catalytic ratio of 1/1000 with respect to the enzyme/substrate net weight was used.



Scheme 2. Kinetic resolution of *rac*-**2** under optimized conditions.

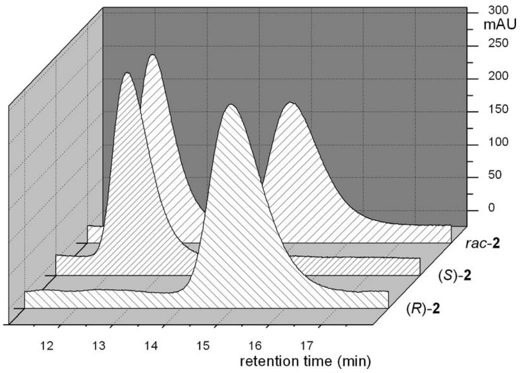
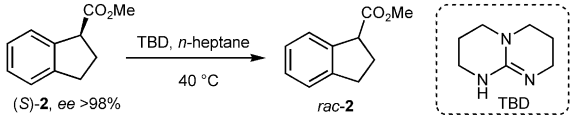


Figure 2. HPLC trace of the kinetic resolution of *rac*-**2** after 4 h [line 1: unreacted substrate *rac*-**2**; line 2: remaining substrate (*S*)-**2**; line 3: product (*R*)-**1** after derivatisation].

Dynamic Kinetic Resolution

The rate of racemisation can be described either as interconversion of the enantiomers present or as the rate of formation of the racemate.[21] In the search for a suitable base for the subsequent racemisation, enantiopure starting material [(*S*)-**2**, $ee > 98\%$] was used and the loss of *ee* was monitored by HPLC. By consideration of the concentrations of the enantiomers and with $k' = 2k_{\text{rac}}$ (k' = rate constant of interconversion; k_{rac} = rate constant of racemisation), k_{rac} can be determined from the ratio of $ee_{\text{S}}/ee_{\text{S0}}$ (ee_{S0} = initial *ee* value of the enantiomer, ee_{S} at a defined time).[22] Different bases and conditions were tested to examine the racemisation of ester (*S*)-**2** (k_{rac}): enantiopure starting material [(*S*)-**2**, $ee > 98\%$] was treated with different bases [pyridine, triethylamine, 1,8-bis(dimethylamino)naphthalene (proton sponge), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), potassium bis(trimethylsilyl)amide (KHMDS)] at different temperatures (25 °C–60 °C) in *n*-heptane, but either no racemisation or only moderate racemisation could be detected. Finally, upon screening for a more efficient base, triazabicyclo-1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) gave the desired results. TBD is a strong bicyclic guanidine base that allows the controlled racemisation of the substrate (*S*)-**2** without affecting the ester function in any way (Scheme 3). The rate of racemisation was determined to be a function of the amount of base (Figure 3): although hardly any racemisation was observed at a low concentration (0.02 equiv.) of TBD (with unreliable data at prolonged reaction times), an increase in the amount of base resulted in a decrease in the ee_{S} value and consequently in racemisation. It was found that 0.13 equiv. of base were ideal to achieve complete racemisation within 2 hours at 40 °C. With the obtained data, the racemisation constant (k_{rac}) as a function of the amount of base was calculated, giving $k_{\text{rac}}/c_{\text{TBD}} \approx 1.6\ (\text{mM h})^{-1}$ (Figure 4). For comparison, for the racemisation of Naproxen[6] or Suprofen[7] the corresponding values (trioctylamine as base) were determined to be $2.5 \times 10^{-4}\ (\text{mM h})^{-1}$ and $8.6 \times 10^{-3}\ (\text{mM h})^{-1}$, respectively.



Scheme 3. Controlled racemisation of (*S*)-**2** in the presence of TBD as base.

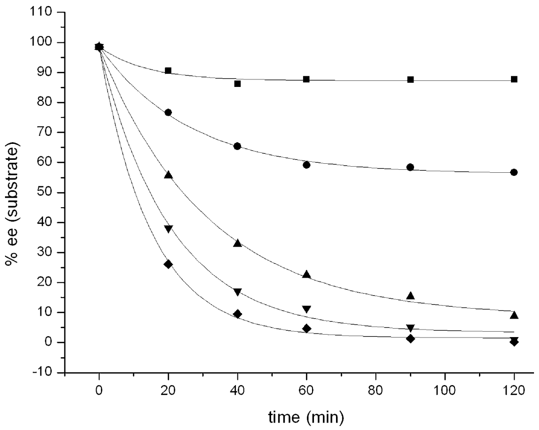


Figure 3. Racemisation of (*S*)-**2** (7.6 mM) as function of base (TBD; analytical scale). Base concentration (mM) (■) = 0.12, (●) = 0.24, (▲) = 0.48, (▼) = 0.72 and (♦) = 0.96. (–) calculated.

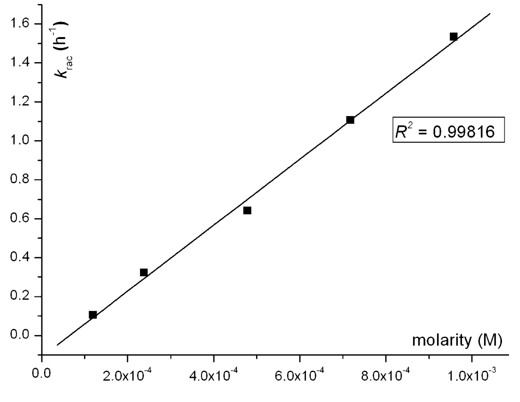
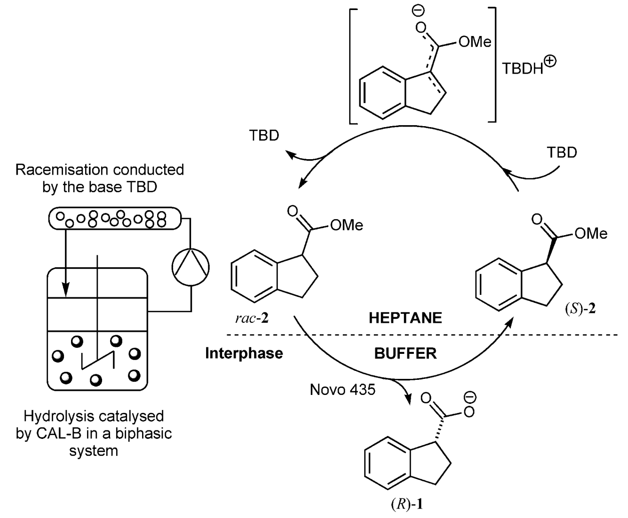


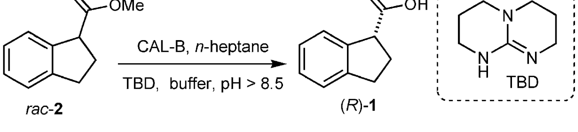
Figure 4. Racemisation constant (k_{rac}) dependence on the c(base).

Because a one-pot system was ineligible for our purpose, a reaction setup that allowed the controlled racemisation of ester **2** in the absence of acid **1** was used. A standard reaction flask was connected with a peristaltic pump to close a circuit with a pre-prepared syringe as shown in Scheme 4. For the investigation of the DKR we decided to apply the biphasic system under basic conditions (buffer pH > 8.5) and with *n*-heptane as organic solvent. Under these conditions the produced acid and the enzyme were kept in the aqueous layer, while the ester (in the organic layer) was continuously pumped through the packed syringe in which racemisation occurred. With this system a combination of the enzymatic hydrolysis with a chemical racemisation technique was achieved.



Scheme 4. Process flowsheet of the reaction setup and the basic principle of the dynamic kinetic resolution.

In order to avoid unpredictable side-reactions and possible enzyme inactivation through base leaching, we added a second layer consisting of a weak cation-exchange resin. The technique was possible because the solubility of the TBD in *n*-heptane is very low. Obviously, with the given setup the transformation could not be performed at elevated temperature because the base would be dissolved more rapidly. We therefore established conditions under which the reaction temperature was kept at 20 °C (room temp.), despite the fact that larger amounts of base were now required. Our initial result at preparative scale (1.00 g, 5.67 mmol of ester **2**) was rather promising, because the required product (*R*)-**1** could be isolated in good yield and a respectable 96% *ee*, already demonstrating dynamic kinetic resolution (Scheme 5, Entry 1). The fact that the remaining ester (*S*)-**2** had an *ee* > 99% indicated either that the racemisation was too slow or that the amount of base was too low. Prolonging the reaction time led to an increased yield, but the *ee* of the product (*R*)-**1** was decreased (*ee* > 90%); again, the *ee* of ester **2** was still high (*ee* > 99%, Entry 2). Consequently, we next added more base (Entries 3 and 4) to increase the rate of racemisation. The best results were obtained with 1.20 equiv. and an extended reaction time of



Entry	Time	Equiv. (TBD)	*ee* (*R*)-**1**	Yeld (*R*)-**1**	*ee* (*S*)-**2**
1	6 h	0.63	> 96%	> 82%	> 99%
2	10 h	0.63	> 90%	> 90%	> 99%
3	4 h	1.00	< 96 %	> 87%	< 42%
4	4 h	1.20	> 96%	< 92%	< 60%
5	10 h	1.20	< 97 %	> 95 %	< 32 %

Scheme 5. Results of the dynamic kinetic resolution of *rac*-**2** with the reaction setup as depicted in Scheme 4.

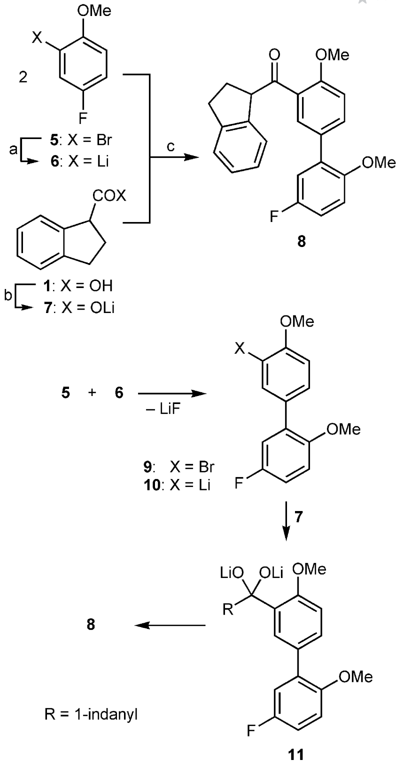
10 h (Entry 5): the desired acid (*R*)-**1** could be isolated in good yield (95%) and high optical purity (*ee* > 96%). It was also demonstrated that stirring had an influence: the relatively high *ee* of ester **2** (*ee* > 60%, Entry 4) was observed upon vigorous stirring (1400 rpm) whereas under "milder reaction conditions" (1000 rpm) the reaction time was increased, but the overall process was more efficient.

Application

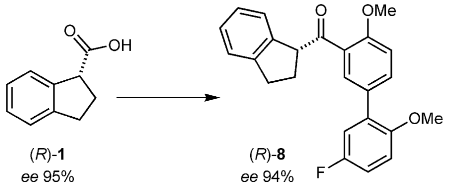
Aryl indan-1-yl ketones have recently[10] proved to be efficient, cell-penetrating, reversible inhibitors of human Pin1, an enzyme that belongs to the family of peptidyl-prolyl-*cis*/*trans*-isomerases (PPIases). They catalyse the rotation of the N-terminal peptide bond in front of proline and have an impact on slow processes involved in protein folding.[23] A series of aryl indanyl ketones prepared from racemic acid **1** displayed remarkable inhibition of Pin1 with inhibition constants in the sub-micromolar range. In the course of the syntheses of various substituted aryl indanyl ketones by treatment of aryllithium compounds with the lithium salt of the acid **1**, an unexpected domino reaction was observed (Scheme 6): when two equivalents of the aryllithium reagent **6**, generated by bromine/lithium exchange from aryl bromide **5**, were allowed to react with lithium carboxylate **7** in diethyl ether, the formation of the biaryl 1-indanyl ketone **8** resulted. Although the yield was moderate (21%), ketone **8** was found to be the only product, apart from recovered carboxylic acid **1** and biaryls. Remarkably, the product turned out to be a single regioisomer, the structure of which was corroborated by a crystal structure analysis of a subsequent product.[10]

In this domino reaction, not only did the expected formation of the aryl–carbonyl bond occur, but it was also accompanied by a completely regioselective aryl–aryl coupling through nucleophilic aromatic substitution. In explanation, we propose that as soon as the aryllithium intermediate **6** forms, it adds to the remaining starting material **5** in the *ipso*-position to the fluorine followed by the elimination of lithium fluoride. Another *n*-butyllithium-induced bromine/lithium exchange then takes place in the biaryl compound **9** to give the nucleophilic aryllithium reagent **10**, which finally attacks the carboxylate **7** to deliver, through the dilithium intermediate **11**, ketone **8** after aqueous acidic workup. Evidence for this interpretation is provided by the observation that, in a reaction between the aryl bromide **5** and *n*-butyllithium in the absence of carboxylate **7**, biphenyl **9** (X = H) is produced, obviously after protonation of the assumed intermediate **10**.[24]

Inhibition of PPIases has been shown in a particular case to depend significantly on the configuration of the stereogenic centre in the monoaryl indanyl ketone,[10] so we were interested in whether the domino reaction would lead to enantiomerically pure biaryl indanyl ketone despite the strongly basic conditions, which could lead to racemization at the α-carbonyl position due to enolate formation. (*R*)-Indane-1-carboxylic acid (**1**) with an optical purity of 95% *ee* was thus subjected to the above domino reaction protocol. We were pleased to find that ketone (*R*)-**8** displayed an enantiomeric excess of 94% *ee*, as shown by chiral HPLC (Scheme 7). This result clearly shows that only insignificant racemization had occurred during the domino reaction.



Scheme 6. Domino reaction for the formation of the biaryl 1-indanyl ketone **8** and proposed explanation for its formation through intermediates **9**, **10** and **11**. Reagents and conditions: a) *n*BuLi, Et$_2$O, –78 °C; b) *n*BuLi, Et$_2$O, –78 °C to 0 °C; c) –78 °C to reflux; 21–27%.



Scheme 7. Synthesis of (*R*)-**8** from (*R*)-carboxylic acid **1**.

Conclusions

In conclusion, we have developed an efficient route to both enantiomers of 2,3-dihydro-1*H*-indene-1-carboxylic acid (**1**) by utilizing enzymatic kinetic resolution (*E* > 100). Furthermore, a new reaction setup for dynamic kinetic resolution was established; the system allowed controlled racemisation, giving an excellent yield (95%) of a highly enantiomerically enriched product (*ee* < 97%) on a preparative scale within a short reaction time. Enantiomerically pure indane carboxylic acid (*R*)-**1** proved to be a valuable starting material from which to obtain the biaryl indan-1-yl ketone **8** with high enantiomeric excess for the first time. The inhibitory potencies and biological activities of (*R*)-**8** and various compounds derived from it will be disclosed in a forthcoming publication.

Experimental Section

General: All starting materials were purchased from commercial suppliers and were used as received, unless stated otherwise. All solvents were dried by common methods prior to use; THF and diethyl ether were freshly distilled from sodium/benzophenone and methanol from calcium hydride. Hydrolases were used in the form of their powders as purchased.

Preparative chromatographic separations were performed by column chromatography on Merck silica gel 60 (0.063–0.200 µm). Solvents for flash chromatography (petroleum ether/ethyl acetate) were distilled before use. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. Tlc was carried out with precoated plastic sheets (Polygram® SIL G/UV, Macherey–Nagel) with detection by UV (254 nm) and/or by staining with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), concd. sulfuric acid (60 mL), H_2O (940 mL)]. Optical rotations were measured at 20 °C with a Perkin–Elmer Polarimeter 241 MC instrument against the sodium D line. ^{1}H and ^{13}C NMR spectra were recorded at 20 °C with a Bruker Avance/DRX 600 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts are given in ppm relative to Me_4Si (^{1}H, Me_4Si = 0 ppm) or to the resonance of the solvent (^{13}C: $CDCl_3$ = 77.0 ppm).

1*H*-Indene-3-carboxylic Acid (4): Indene (**3**, 10.0 g, 86.1 mmol) was diluted with dry THF (86 mL) and cooled to –78 °C as described in ref.[25] *n*BuLi (56.5 mL of a 1.6 M solution in THF, 90.4 mmol) was added dropwise over 30 min. The resulting orange mixture was stirred for 30 min at 0 °C and cooled to –78 °C, after which crushed dry ice (200 g) was placed directly into the reaction vessel. The mixture was allowed to warm to room temperature overnight. After acidification to pH 2 with aqueous HCl (2 N), the mixture was extracted with EtOAc (4 × 50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography on silica [eluent petroleum ether/ethyl acetate (95:5 to 70:30) (+ 1 vol.-% acetic acid)] afforded the acid **4** as a colourless powder (11.6 g, 72.6 mmol, 84 %). The data are fully in agreement with those reported in ref.[25] M.p. 161–162 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.59 (d, $^3J_{1,2}$ = 1.7 Hz, 2 H, 1-H), 7.30 (m, 1 H, arom.-H), 7.38 (m, 1 H, arom.-H), 7.51 (m, 1 H, arom.-H), 7.65 (t, $^3J_{2,1}$ = 1.9 Hz, 1 H, 2-H), 8.09 (m, 1 H, arom.-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 38.7 (C-1), 122.5 (arom.-CH), 123.9 (arom.-CH), 125.8 (arom.-CH), 126.8 (arom.-CH), 135.7 (C-2), 140.4 (C-3), 143.3 (arom.-C_{ipso}), 147.2 (arom.-C_{ipso}), 169.3 (C-1′) ppm. IR (ATR film): $\tilde{\nu}_{max}$ = 3044, 2891, 2780, 2603, 1679 (C=O), 1257, 905, 770 cm^{-1}. GC-MS (EI, 70 eV): *m*/*z* (%) = 115 (100) $[M - CO_2]^+$. $C_{10}H_8O_2$ (160.17): calcd. C 74.99, H 5.03; found C 74.84, H 5.18.

2,3-Dihydro-1*H*-indene-1-carboxylic Acid (1): Indene-1*H*-carboxylic acid (**4**, 11.6 g, 72.6 mmol) was dissolved in dry MeOH (3 mL mmol^{-1}), after which Pd/C (0.77 g, 7.3 mmol) was carefully added. The mixture was stirred vigorously and the flask was then evacuated and flushed with hydrogen at least five times. Stirring under H_2 was continued overnight. After complete conversion was observed (as judged by tlc) the mixture was filtered through a plug of Celite 545®, washed with MeOH and concentrated under reduced pressure. Subsequent filter flash column chromatography {eluent petroleum ether/ethyl acetate (90:10) [+ 1 vol.-% acetic acid]} furnished the desired acid as a colourless powder (11.5 g, 71.2 mmol) in 98 % yield. The obtained data are fully in agreement with those reported in ref.[26] M.p. 53–54 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.35 (dddd, $^3J_{3a,2}$ = 6.0, $^3J_{3a,4a}$ = 6.1, $^3J_{3a,4b}$ = 8.6, $^2J_{3a,3b}$ = 14.7 Hz, 1 H, 3-H_a), 2.43 (dddd, $^3J_{3b,4b}$ = 6.1, $^3J_{3b,2}$ = 8.7, $^3J_{3b,4a}$ = 8.7, $^2J_{3b,3a}$ = 14.8 Hz, 1 H, 3-H_b), 2.92 (ddd, $^3J_{4a,3a}$ = 6.2, $^3J_{4a,3b}$ = 8.8, $^2J_{4a,4b}$ = 15.2 Hz, 1 H, 4-H_a), 3.10 (ddd, $^3J_{4b,3b}$ = 6.1, $^3J_{4b,3a}$ = 8.7, $^2J_{4b,4a}$ = 15.3 Hz, 1 H, 4-H_b), 4.07 (dd, $^3J_{2,3a}$ = 6.0, $^3J_{2,3b}$ = 8.5 Hz, 1 H, 2-H), 7.16–7.26 (m, 3 H, arom.-H) 7.42 (m_c, 1 H, arom.-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.6 (C-3), 31.7 (C-2), 50.0 (C-1), 124.7 (arom.-CH), 124.9 (arom.-CH), 126.5 (arom.-CH), 127.8 (arom.-CH), 140.0 (arom.-C_{ipso}), 144.2 (arom.-C_{ipso}), 180.5 (C-1′) ppm. IR (ATR film): $\tilde{\nu}_{max}$ = 3023, 2919, 2850, 2611, 1711 (C=O), 1417, 1281, 1225, 939, 736 cm^{-1}. GC-MS (EI, 70 eV): *m*/*z* (%) = 162 (29) $[M]^+$, 117 (100) $[M - CO_2]^+$. $C_{10}H_{10}O_2$ (162.19): calcd. C 74.06, H 6.21; found C 73.99, H 6.22.

Methyl 2,3-Dihydro-1*H*-indene-1-carboxylate (2): The acid **1** (10.2 g, 62.9 mmol) was dissolved in dry MeOH (10 mL mmol^{-1}) and a few drops of concd. H_2SO_4 were added. The mixture was heated at reflux until no starting material could be detected (as judged by tlc; up to 72 h). The solution was then allowed to cool down to room temperature, concentrated under reduced pressure and extracted four times with EtOAc (4 × 30 mL) against saturated $NaHCO_3$ solution (300 mL). The combined organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography on silica (eluent petroleum ether/ethyl acetate, 99:1) gave the desired ester **2** in 92 % yield (10.2 g, 57.9 mmol) and as a colourless liquid. The spectroscopic data are fully in agreement with those reported in ref.[27] ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.34 (dddd, $^3J_{3a,2}$ = 5.8, $^3J_{3a,4b}$ = 5.8, $^3J_{3a,4a}$ = 8.6, $^2J_{3a,3b}$ = 12.9 Hz, 1 H, 3-H_a), 2.44 (dddd, $^3J_{3b,4a}$ = 6.4, $^3J_{3b,2}$ = 8.8, $^3J_{3b,4b}$ = 8.8, $^2J_{3b,3a}$ = 12.9 Hz, 1 H, 3-H_b), 2.91 (ddd, $^3J_{4a,3b}$ = 6.5, $^3J_{4a,3a}$ = 8.7, $^2J_{4a,4b}$ = 15.2 Hz, 1 H, 4-H_a), 3.10 (ddd, $^3J_{4b,3a}$ = 5.8, $^3J_{4b,3b}$ = 8.8, $^2J_{4a,4b}$ = 15.3 Hz, 1 H, 4-H_b), 3.73 (s, 1 H, OMe), 4.06 (dd, $^3J_{2,3a}$ = 6.2, $^3J_{2,3b}$ = 8.4 Hz, 1 H, 2-H), 7.16–7.26 (m, 3 H, arom.-H), 7.37 (m_c, 1 H, arom.-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.9 (C-3), 34.1 (C-2), 49.9 (C-1), 52.0 (COO*Me*), 124.7 (arom.-CH), 124.8 (arom.-CH), 126.4 (arom.-CH), 127.6 (arom.-CH), 140.7 (arom.-C_{ipso}), 144.1 (arom.-C_{ipso}), 174.4 (C-1′) ppm. IR (ATR film): $\tilde{\nu}_{max}$ = 2951, 1732 (C=O), 1477, 1434, 1210, 1194, 1166, 1023, 983, 745 cm^{-1}. GC-MS (EI, 70 eV): *m*/*z* (%) = 176 (26) $[M]^+$, 117 (100) $[C_9H_9]^+$. $C_{11}H_{12}O_2$ (176.21): calcd. C 74.98, H 6.86; found C 74.91, H 6.85.

Procedure for the Enzyme Screening of *rac*-2: An aliquot (1 mL) was taken from a stock solution of the enzyme (1 mg mL^{-1}) in KPi Buffer (100 mM, pH 8.0) and added to the substrate (2 mg in *n*-heptane, 1 mL) in a 2 mL Eppendorf vial. The reaction mixture was vigorously shaken on a Thermomix (Eppendorf) at 40 °C and 1400 upm. After defined periods of time (3 h, 26 h) aliquots (15 µL) were taken from the organic layer, diluted with *n*-heptane (300 µL) and extracted against saturated aqueous $NaHCO_3$ solution (500 µL). After effervescence had ceased and the layers had separated, the organic phase (150 µL) was taken and analysed by HPLC on a chiral stationary phase (injection volume: 10 µL). Conditions: HPLC: column = Chiracel OB (Daicel), average: 0.46 cm, length: 25 cm, flow = 0.65 mL min^{-1}, λ = 202 nm, solvent ratio = 98:2 (*n*-heptane/2-propanol), t_R[(*R*)-**2**] = 13.4 min and t_R[(*S*)-**2**] = 16.4 min.

Procedure for the Medium Engineering of *rac*-2: An aliquot (1 mL) was taken from a stock solution of CAL-B (1 mg mL^{-1}) in KPi Buffer (100 mM, pH 8.0) and added to the substrate (2 mg in organic solvent, 1 mL, as depicted in Scheme 3) in a 2 mL Eppendorf vial. The reaction mixture was vigorously shaken on a Thermomix (Eppendorf) at defined temperature (Table 2) and 1400 upm. After defined periods of time (5 min, 10 min, 15 min, 20 min, 30 min, ..., 90 min), aliquots (15 µL) were taken from the organic layer, diluted with *n*-heptane (300 µL) and extracted against saturated aqueous NaHCO$_3$ solution (500 µL). After effervescence had ceased and the layers had separated, the organic phase (150 µL) was taken and analysed by HPLC on a chiral stationary phase (injection volume: 10 µL; vide supra). The remaining aqueous phase was acidified to pH 1.0 with a stock HCl solution (2 M in water) and extracted with EtOAc (300 µL). The organic layer (150 µL) was taken and analysed by GC on a chiral stationary phase (injection volume: 5 µL). Conditions: GC column: FS cyclodex β IP, carrier gas: hydrogen, temperature program: 150 °C to 195 °C with slope 2.5 °C min^{-1}, t_R[(*S*)-**1**] = 15.1 min, t_R[(*R*)-**1**] = 15.5 min. Alternatively the organic layer could be treated with diazomethane solution in ether to yield ester (*R*)-**2**; the solvent was removed and the residue was redissolved in *n*-heptane and measured on HPLC (vide supra).

Enzymatic Esterification of *rac*-1: A stock solution of CAL-B (0.2 mg in 0.9 mL of KPi buffer, 100 mM, pH 3.4) was prepared. MeOH (100 µL) and substrate ***rac*-1** (stock solution: 2 mg in organic solvent as outlined in Scheme 5) were added. The reaction mixture was vigorously shaken on a Thermomix (Eppendorf) at 40 °C and 1400 upm. Aliquots (15 µL) were taken from the organic layer at 10 min time intervals, diluted with *n*-heptane (300 µL) and extracted against saturated aqueous NaHCO$_3$ solution (500 µL). After effervescence had ceased and the layers had separated, the organic phase (150 µL) was taken and analysed by HPLC on a chiral stationary phase (injection volume: 10 µL; vide supra). The remaining aqueous phase was acidified to pH 1.0 with a stock HCl solution (2 M in water) and extracted with EtOAc (300 µL). The organic phase (150 µL) was taken and analysed by GC on a chiral stationary phase (injection volume: 5 µL; vide supra).

Lipase-Catalysed Kinetic Resolution of *rac*-2: The ester ***rac*-2** (2.00 g, 11.35 mmol) was diluted with a potassium phosphate buffer (100 mM, pH = 8.0, 20 mL) in a two-necked 50 mL reaction flask. The setup was provided with a pH electrode and a stirring bar, after which immobilized *Candida antarctica* lipase B (Novo435, 100 mg)[17] was added. The pH was maintained at pH 8.0 during the reaction by addition of small portions of NaOH solution (2 M). After the substrate had reached an *ee* of >95% (determined by HPLC; approx. 4–5 h) the solution was filtered through a plug of cotton and extracted three times with Et$_2$O (3 × 30 mL). The remaining aqueous phase was acidified to pH 2.5 with HCl solution (2 M in water) and also extracted three times with EtOAc (3 × 30 mL). The combined organic layer was dried with MgSO$_4$, filtered and concentrated under reduced pressure. Subsequent chromatography {eluent PE/ethyl acetate (98:2 to 80:20) [+ 1 vol.-% acetic acid]} afforded the ester (*S*)-**2** (0.98 g, 49%, 5.56 mmol) as a colourless liquid and the acid (*R*)-**1** (0.79 g, 4.89 mmol) in 43% yield as a colourless powder. Spectroscopic data are identical with those reported for each compound. Optical rotation for (*R*)-**1**: $[a]_D^{25}$ = +40.6 (*c* = 7.5, benzene, *ee* > 97%); lit.[27] value: $[a]_D^{25}$ = +43.3 (*c* = 0.026, benzene) and for (*S*)-**2**: $[a]_D^{20}$ = +1.5 (*c* = 3.1, ethanol, *ee* > 99%); lit.[16] value: $[a]_D^{20}$ = +0.5 (*c* = 2.5, ethanol).

Acid-Promoted Hydrolysis of Methyl (*S*)-2,3-Dihydro-1*H*-indene-1-carboxylate [(*S*)-2]: An aqueous HCl stock solution (2 N, 315 µL) was added to a stirred solution of the ester (*S*)-**2** (110 mg, 627 µmol, *ee* > 97%) in dry THF (7 mL). The mixture was stirred vigorously for four days at room temperature, diluted with water (20 mL) and extracted four times with EtOAc (4 × 5 mL). Combined organic layers were dried with MgSO$_4$, filtered and concentrated under reduced pressure. Subsequent column chromatography {eluent petroleum ether/ethyl acetate (95:5) [+ 1vol.-% acetic acid]} afforded the remaining ester (*S*)-**2** (45 mg, 257 µmol, 23%, *ee* > 97%) and the acid (*S*)-**1** (62 mg, 386 µmol, 62%, *ee* >97%). Spectroscopic data are identical with those reported for each compound. Optical rotation for (*S*)-**1**: $[a]_D^{25}$ = –42.4 (*c* = 1.0, benzene); lit.[28] value: $[a]_D^{25}$ = +43.3 [*c* = 0.026, benzene, for the *R* enantiomer].

Determination of the Racemisation Constant (k_{rac}): Defined aliquots (25 µL, 50 µL, 100 µL, 150 µL, 200 µL) were taken from a stock solution of TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene, 1 mg mL^{-1} in *n*-heptane), added to a substrate stock solution [(*S*)-**2**, 2 µL in 1 mL *n*-heptane, *ee* > 98%] and diluted with *n*-heptane to reach a total volume of 1.5 mL in an Eppendorf vial. The mixture was shaken on a Thermomix (Eppendorf) at 40 °C and 1400 rpm and after defined periods of time (20 min, 40 min, 60 min, 90 min and 120 min) small samples (15 µL) were taken, filled up with further *n*-heptane (100 µL) and measured by chiral HPLC as described. For further information on racemisation see ref.[21]

Dynamic Kinetic Resolution of Methyl 2,3-Dihydro-1*H*-indene-1-carboxylate [*rac*-2]

General Information: The reaction setup is depicted in Figure 3. Before the DKR was started a 5 mL syringe was prepared as follows: cotton wool was placed at the bottom, followed by the cation-exchange resin (Merck, Amberlite®, IRC-50, 20–50 mesh, 2.00 g). Another layer of cotton wool and the unlinked base TBD (948 mg, 6.81 mmol) were added afterwards. The syringe was capped with a third layer of cotton and was now ready to use.

Racemic ester **2** (1.00 g, 0.68 mmol) was diluted with *n*-heptane (20 mL) in a three-necked reaction flask and stirred until a homogeneous phase resulted. The buffer solution (100 mM KPi, pH 8.0) and enzyme (100 mg, Novozyme 435) were added while stirring (1200 rpm) was continued. After 5 min a Teflon tube [connected to a peristaltic pump (Pharmacia Bioscience P1) and the pre-packed syringe] was submerged into the organic layer and the pump was run continuously with a flow of 0.5 mL min^{-1} until the reaction was complete. The pH was monitored with a pH electrode and was kept constant at pH 8.0 with an aqueous NaOH stock solution (1 N). After 10 h the theoretical amount of NaOH had been consumed and the reaction was stopped by filtering off the enzyme through a plug of cotton wool. The mixture was acidified to pH 2.0 with an aqueous HCl stock solution (2 N) and extracted five times with EtOAc (5 × 20 mL). The combined organic layer was dried with MgSO$_4$, filtered and concentrated under reduced pressure. Column chromatography {eluent petroleum ether/ethyl acetate (98:2 to 80:20) [+ 1vol.-% acetic acid]} gave a small amount of the remaining ester (*S*)-**2** (15 mg, 85 µmol, 2%, *ee* < 32%) and the desired acid (*R*)-**1** (874 mg, 5.38 mmol, 95%, *ee* < 97%). Spectroscopic data are identical with those reported above.

(*R*)-(5′-Fluoro-2′,4-dimethoxybiphenyl-3-yl)indan-1-yl-methanone (*R*)-8: Under dry nitrogen, a 25 mL two-necked flask was provided with a magnetic stirrer and a connection to a combined nitrogen/vacuum line and closed with a septum. The air in the flask was replaced by nitrogen, and anisole **5** (1.22 g, 6.03 mmol) and dry diethyl ether (8 mL) were injected by syringe. After the system had been cooled to –78 °C in a dry-ice/acetone bath, a solution of *n*BuLi in hexane (1.6 M, 4.2 mL, 6.7 mmol) was added dropwise by syringe, and stirring was continued for 20 min at the same temperature.

In a second, similarly fitted flask, carboxylic acid (*R*)-**1** (480 mg, 2.95 mmol) was dissolved under nitrogen in diethyl ether (11 mL) and cooled to –78 °C. A solution of *n*BuLi in hexane (1.6 M, 4.2 mL, 6.7 mmol) was added by syringe. The mixture was then allowed to reach –20 °C, and the stirred solution in the first flask was then added through a cannula. The mixture was allowed to warm to room temperature overnight and was then heated gently at reflux for 1 h. After the system had cooled to room temperature, water (5 mL) and HCl (2 N, 5 mL) were added. The aqueous layer was separated and extracted three times with three portions of Et_2O (50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed in a rotary evaporator and the residue was subjected to column chromatography on silica gel with chloroform to give (*R*)-**8** (231 mg, 0.61 mmol, 21 %) as a yellowish oil. R_f = 0.29 (chloroform). $[\alpha]_D^{20}$ = +20.0 (*c* = 1.08, $CHCl_3$); HPLC: column = Chirapak AS, average: 0.46 cm, length: 25 cm, flow = 1.0 mL min^{-1}, λ = 225 nm, solvent ratio = 99:1 (*n*-heptane/2-propanol), t_R[(*S*)-**8**] = 14.8 min and t_R[(*R*)-**8**] = 18.3 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36–2.52 (m, 2 H, CH_2), 2.91–3.14 (m, 2 H, CH_2), 3.76 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 5.10 (dd, J_1 = 5.93, J_2 = 8.41 Hz, 1 H, CO-C*H*), 6.88 (dd, $^3J_{3',4'}$ = 8.96, $^4J_{3',F}$ = 4.54 Hz, 1 H, 3′-H), 6.97 (ddd, $^3J_{4',3'}$ = 8.71, $^3J_{4',F}$ = 8.04, $^4J_{4',6'}$ = 3.16 Hz, 1 H, 4′-H), 7.02 (dd, $^3J_{6',F}$ = 9.10, $^4J_{6',4'}$ = 3.12 Hz, 1 H, 6′-H), 7.05 (d, $^3J_{5,6}$ = 8.63 Hz, 1 H, 5-H), 7.66 (dd, $^3J_{6,5}$ = 8.63, $^4J_{6,2}$ = 2.37 Hz, 1 H, 6-H), 7.72 (d, $^4J_{2,6}$ = 2.31 Hz, 1 H, 2-H), 7.06–7.28 (m, 4 H, arom-CH, indanyl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.3 (C-2, indanyl), 31.9 (C-3, indanyl), 55.7 (OMe), 56.2 (OMe), 57.0 (CO*C*H), 111.3, 124.6, 125.1, 126.1, 127.1, 128.6, 131.4, 133.9, 142.1, 144.7, 157.4 (arom.-CH, without fluoro coupling), 112.7, 114.7, 117.5, 130.4, 131.0, 153.0, 157.5 (arom.-CH, with fluoro coupling), 203.7 (CO) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –124.3 (ddd, $^3J_{F,6'}$ = 8.55, $^3J_{F,4'}$ = 8.47, $^4J_{F,3'}$ = 4.62 Hz, 1 F) ppm. GC-MS (EI, 70 eV): *m/z* (%) = 376 (6) [M]$^+$, 259 (100) [$C_{15}H_{12}O_3F$]$^+$.

Supporting Information (see also the footnote on the first page of this article): A complete list of enzymes screened for the kinetic enzymatic resolution.

Acknowledgments

We gratefully acknowledge the Deutsche Forschungsgemeinschaft (DFG) and Ministry of Innovation, Science, Research and Technology of the German federal state of North Rhine-Westphalia for the generous support of our projects. Donations from BASF AG, Boehringer Mannheim GmbH (now Roche diagnostics), Chemetall GmbH, Cognis GmbH, Julich Chiral Solutions GmbH (now Codexis), and Wacker AG were greatly appreciated.

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[24] The major side product was found to be 5,5′-difluoro-2,2′-dimethoxybiphenyl, which obviously is formed by Wurtz-type coupling of bromide **5** and aryllithium intermediate **6**. Its formation seems to be the major reason for the low yield in the domino reaction.

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Received: September 8, 2009