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Temperature-Controlled Bidirectional Enantioselectivity in a Dynamic Catalyst for Asymmetric Hydrogenation**

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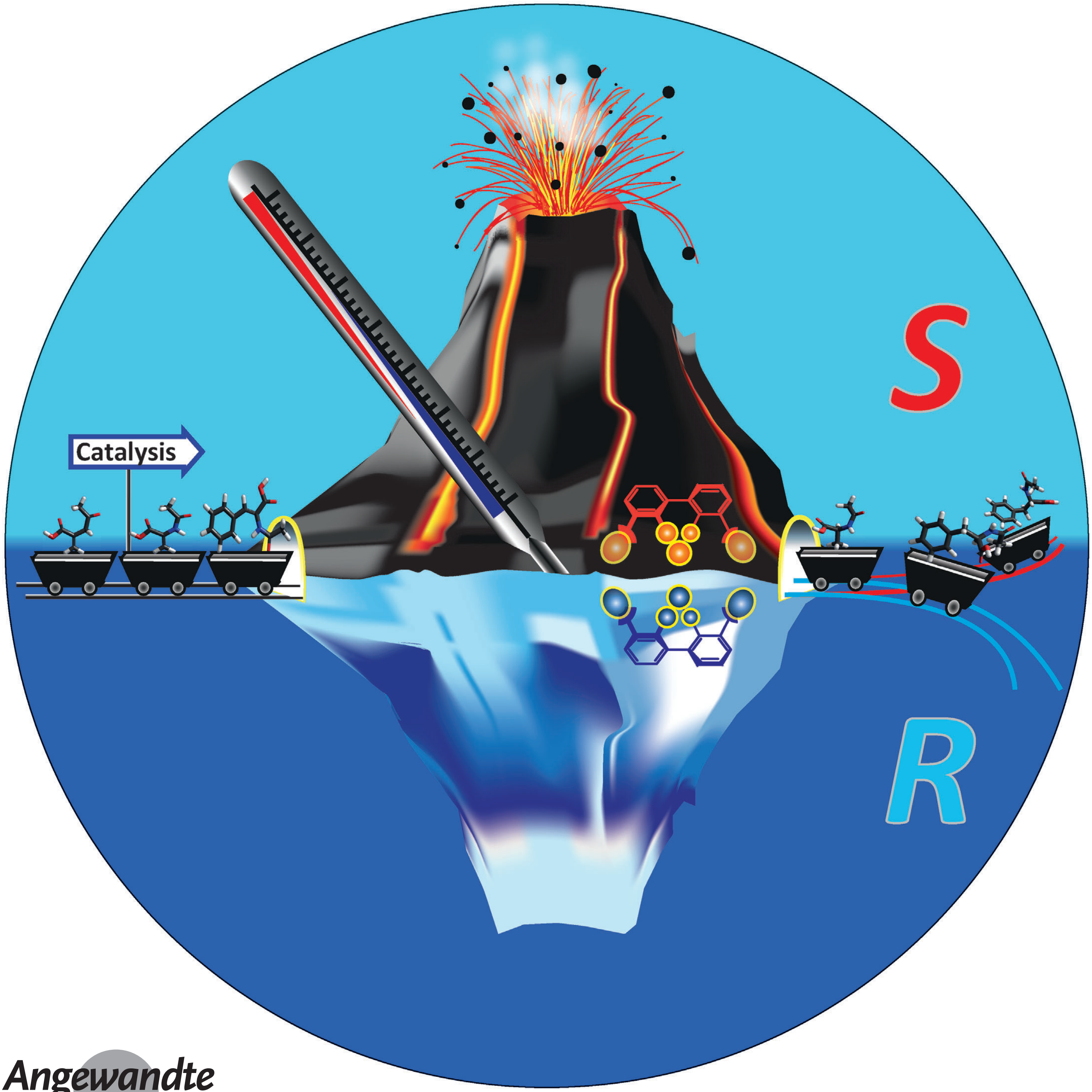

Abstract: *Asymmetric catalysis using enantiomerically pure catalysts is one of the most widely used methods for the preparation of enantiomerically pure compounds. The separate synthesis of both enantiomerically pure compounds requires tedious and time-consuming preparation of both enantiomerically pure catalysts or chiral separation of the racemic products. Here, we report a stereochemically flexible diastereomeric rhodium(I) catalyst for asymmetric hydrogenations of prochiral (Z)-α-acetamidocinnamates and α-substituted acrylates, which changes its enantioselectivity depending on the temperature to produce each enantiomerically pure compound in high yield with constant high enantioselectivity over time. The same axially chiral rhodium(I) catalyst produces (R)-phenylalanine derivatives in enantiomeric ratios of up to 87:13 (R/S) at low temperature and up to 3:97 (R/S) of the corresponding S enantiomers after re-equilibration of the same catalyst at elevated temperature.*

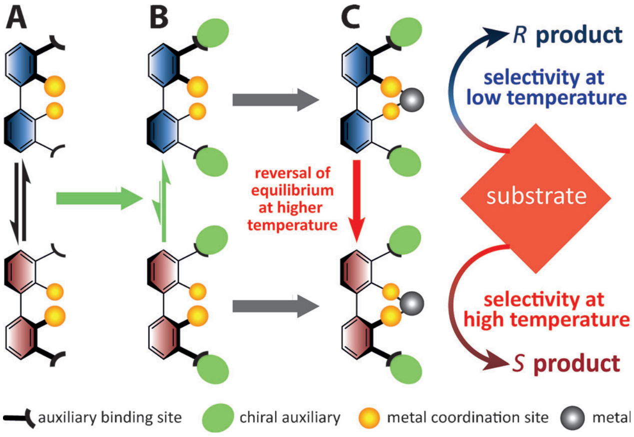

Figure 1. Design of a bidirectional enantioselective catalyst that switches enantioselectivity upon changing the temperature. A) A stereochemically flexible ligand core as a chiral switching unit of the catalyst with binding sites to allow modification with a chiral auxiliary and coordination of metals. B) Chemical bonding of a chiral auxiliary shifts the equilibrium as a consequence of diastereomer formation. C) Catalyst formation by coordinating a metal precursor to the ligand core. The equilibrium ratio of the metal-fixed diastereomeric catalysts can be altered by changing the temperature. The asymmetric catalysis of prochiral substrates leads to either *R* or *S* products.

Asymmetric hydrogenation constitutes one of the most widely used reactions to synthesize enantiomerically pure compounds, for example, the Parkinson's drug L-3,4-dihydroxyphenylalanine (L-DOPA).[1–3] Enantiopure and stereochemically rigid catalysts are used for this purpose. The synthesis of these catalysts remains a tedious and expensive task. In particular, pharmacological studies often require both enantiomers to investigate potentially different activities and side effects. One concept to facilitate this cumbersome process is to use catalysts with stereochemically flexible ligands,[4] for example, tropos biphenyls, in combination with a suitable activator that forms a diastereomeric complex with the catalyst and shifts the equilibrium to one of the ligand enantiomers.[5–11] Upon hydrogenation, this activator is irreversibly removed to generate free coordination sites.[12] Initially, this yields enantiomerically enriched hydrogenation products, yet over the course of the reaction the racemization of the catalyst leads to a depletion of the net enantioselectivity.[13] However, the opposite activator is required to obtain the opposite product enantiomer, because the configuration of the activator controls the product's chirality. Together with the elaborate synthesis and selection of the chiral activator, this constitutes one of the major drawbacks of this elegant approach.

In an effort to overcome the above-mentioned limitations we developed a catalytic system with a tropos 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP) ligand as a stereochemically flexible ligand core to enable switching of the catalyst's enantioselectivity (Figure 1 A). BINAP, the stereochemically rigid atropos parent ligand, is a widely used chiral ligand in asymmetric catalysis.[14] The enantioselectivity of BINAP-type catalysts is controlled by the torsion angle of the biaryl and the alignment of the phenyl groups at the phosphine atom binding to the metal center. In the present study we modified the tropos ligand core with a homochiral auxiliary substituent as the chiral directing group (Figure 1 B).

The ligand core was modified with binding sites to attach readily available chiral auxiliaries to form a pair of diastereomeric complexes (Figure 1 B). By binding the auxiliary to the ligand's core, the chiral information is continuously transferred to the stereochemically flexible chiral axis of the tropos biphenyl, which shifts the stereoisomeric ratio away from the 1:1 equilibrium. The catalyst is formed by coordination of a metal precursor to the pair of diastereomeric ligand cores, which freezes the equilibrium ratio of the stereoisomers, provided a proper auxiliary is chosen (Figure 1 C). In general, the ratio of epimerizing diastereomers can be controlled by external parameters, for example, temperature (Figure 1 C).

The chiral auxiliary has to fulfill the following prerequisites: A stereogenic center close to the linking group that maximizes stereoselective interactions, and an expanded aryl group that aligns the adjacent phenyl rings of the metal-bound diphenylphosphine group.[15] In addition, this auxiliary can be the enantiomerically pure product of a catalytic reaction, thereby making self-amplifying asymmetric processes possible.[16,17]

In a previous study[18] we investigated the stereodynamic properties of BIPHEP ligands depending on the substituents in the *ortho* or *para* position to the diphenylphosphine group. The rotational barrier $\Delta G^{\neq}$ of the biphenyl structure is adjustable between 86 and 101 kJ mol^{-1}, which makes such compounds ideally suited as tropos ligand cores. Rotational

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barriers between 95 and 97 kJ mol^{-1} were measured for simple alkoxy-substituted BIPHEPs. This allows rapid epimerization of the ligand at elevated temperature while maintaining the de novo isomer ratio by cooling below room temperature. Furthermore, we could previously demonstrate that chirality transfer to the stereogenic axis by selector–selectand interactions in the backbone of the BIPHEP ligand leads to partial deracemization and enantioselectivity in asymmetric catalysis.[19]

With the objective of a higher rotational barrier $\Delta G^{\neq}$ of the tropos ligand and a facilitated central-to-axial chirality transfer, which improves the enantioselectivity in the intended catalytic transformation, we introduced hydroxy groups in positions 3 and 3′ of the BIPHEP ligand core by a phospho-Fries rearrangement[13] of 3-bromophenyl diphenylphosphinate. Protection of the hydroxy groups, followed by Ullmann coupling, deprotection, and finally reduction of the phosphine oxides gives stereolabile 2,2′-bis(diphenylphosphino)-[1,1′-biphenyl]-3,3′-diol (3,3′-BIPHEP^{OH}, **1**) as the ligand core (Figure 2 A, see the Supporting Information for experimental details). This compound exists as a 1:1 mixture of interconverting axially chiral enantiomers (R_{ax}/S_{ax}) and hence is racemic. Chemical modification of the tropos ligand core 3,3′-BIPHEP^{OH} (**1**) can be performed in a late synthetic step, which allows convergent large-scale synthesis of the unmodified chiral core and facile preparation of various derivatives.

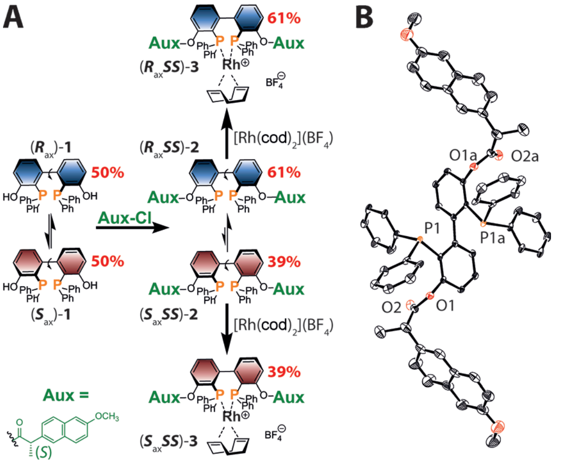


Figure 2. Synthesis of the bidirectional enantioselective catalyst **3**. A) The interconverting tropos 2,2′-bis(diphenylphosphino)-[1,1′-biphenyl]-3,3′-diol (3,3′-BIPHEP^{OH}, **1**) as the chiral ligand core is treated with (*S*)-naproxen as the chiral auxiliary to afford the diastereomeric ligand 3,3′-BIPHEP^{ONap*} (**2**). Tropos ligand **2** is converted into the diastereomeric 3,3′-BIPHEP^{ONap*}Rh^{I} catalysts ($R_{ax}SS$)-**3** and ($S_{ax}SS$)-**3** by using the rhodium precursor [Rh(cod)$_2$](BF$_4$). The diastereomeric ratio of the ligands **2** is retained in the catalysts **3**. B) Molecular structure of ($S_{ax}SS$)-**2** (ellipsoids are shown at the 50% probability level; chloroform molecules and hydrogen atoms are omitted for clarity).[34]

We chose the anti-inflammatory drug (*S*)-naproxen as the auxiliary, which is attached to the phenolic binding sites of 3,3′-BIPHEP^{OH} (**1**). Enantiopure (*S*)-naproxen has an extended aryl moiety and a stereogenic center close to the linking carboxy group. It is readily available in large amounts, thus allowing to easily scale-up the synthesis of the targeted catalyst. This 2-aryl propionic acid can be synthesized by enantioselective hydrogenation and exhibits fascinating properties in relation to deracemization, for example, (*S*)-naproxen can be readily obtained in enantiomerically pure form by Ostwald ripening.[20–22]

Covalently binding the (*S*)-naproxen auxiliary to the stereochemically flexible ligand core 3,3′-BIPHEP^{OH} (**1**) through the ester group (Figure 2 A) yields the modified diastereomeric ligands 3,3′-BIPHEP^{ONap*} ($R_{ax}SS$)-**2** and ($S_{ax}SS$)-**2**. This also results in a shift of the ligands equilibrium ratio ($R_{ax}SS$)-**2** and ($S_{ax}SS$)-**2** from 50:50 to 61:39 as a result of a central-to-axial chirality transfer of the chiral auxiliary to the axially chiral biphenyl core.

To determine the barriers for the epimerization of the tropos diastereomers ($R_{ax}SS$)-**2** to ($S_{ax}SS$)-**2** and vice versa, the single diastereomers were isolated by preparative chiral high-performance liquid chromatography (Chiralpak-IB, separation factor $\alpha = 1.35$). The elution order of ($R_{ax}SS$)-**2** before ($S_{ax}SS$)-**2** was assigned by determining the absolute configuration by X-ray diffraction crystallography (Figure 2 B). The epimerization process was followed by ^{31}P{^{1}H} NMR and ^{1}H NMR spectroscopy of ($R_{ax}SS$)-**2** and ($S_{ax}SS$)-**2** dissolved in CDCl$_3$ under heating to 70 °C (Figures S4–S8). This resulted in rapid re-equilibration to a ($R_{ax}SS$)-**2**/($S_{ax}SS$)-**2** ratio of 61:39, with reaction rate constants and epimerization barriers of $k(R_{ax}SS \rightarrow S_{ax}SS) = 1.06 \times 10^{-4}\,s^{-1}$ and $\Delta G^{\neq} = 110.6\,kJ\,mol^{-1}$, and $k(S_{ax}SS \rightarrow R_{ax}SS) = 1.66 \times 10^{-4}\,s^{-1}$ and $\Delta G^{\neq} = 109.3\,kJ\,mol^{-1}$ (correlation factor $R^2 = 0.986$), respectively. This corresponds to half-lifes τ of 55 and 35 min at 70 °C, respectively. These extended half-lifes of ligands ($R_{ax}SS$)-**2** and ($S_{ax}SS$)-**2** compared to previously reported BIPHEPs[18,19] will already reduce degradation of the enantioselectivity as a result of ligand epimerization during the course of catalysis.

To investigate the catalytic properties of the tropos ligand ($R_{ax}SS$)-**2**/($S_{ax}SS$)-**2**, we prepared the rhodium(I) catalysts ($R_{ax}SS$)-**3** and ($S_{ax}SS$)-**3** (Figure 2 A) to perform asymmetric hydrogenations of prochiral olefins. Thus, the equilibrated ligand mixture ($R_{ax}SS$)-**2**/($S_{ax}SS$)-**2** (61:39) was treated with the rhodium(I) complex [Rh(cod)$_2$](BF$_4$) to yield the corresponding catalyst 3,3′-BIPHEP^{ONap*}Rh^{I} ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** (Figure 2 A) with a retained diastereomeric ratio of 61:39 for ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3**, as determined by ^{31}P{^{1}H} NMR spectroscopy (Figure S12A). It should be mentioned that the diastereomeric ratio is frozen upon complexation of the metal and does not change at room temperature.

Surprisingly, heating the dissolved diastereomeric 3,3′-BIPHEP^{ONap*}Rh^{I} mixture ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** (61:39) to 70 °C prior to catalysis provides the previously minor isomer ($S_{ax}SS$)-**3** in a purity greater than 99 % instead of the initial major rotational diastereomer ($R_{ax}SS$)-**3** obtained from the thermodynamically favored ligand ($R_{ax}SS$)-**2**. Additional kinetic studies were conducted to study the stereoselective auxiliary-controlled depletion of the ($R_{ax}SS$)-**3** catalyst. The diastereomeric Rh^{I} catalysts ($R_{ax}SS$)-**3** and ($S_{ax}SS$)-**3** show two characteristic $^{1}J_{P\text{-}Rh}$ doublets for the individual diastereomers (Figures S9–S11), which we utilized as a probe in

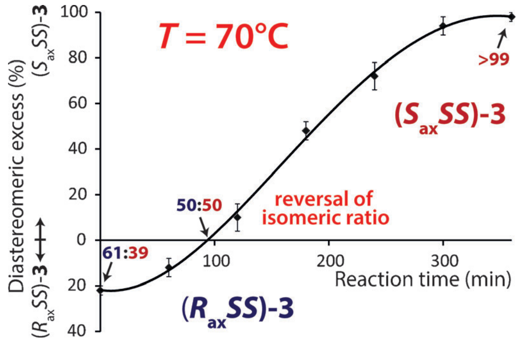


Figure 3. Kinetic profile of the epimerization of diastereomeric Rh^I catalysts $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3** to $(S_{ax}SS)$-**3** upon heating at 70 °C. The diastereomeric ratios were determined by ^{31}P{^{1}H} NMR spectroscopic analysis of the two characteristic $^1J_{P\text{-}Rh}$ doublets of the diastereomers. The originally dominating diastereomeric catalyst $(R_{ax}SS)$-**3** is completely depleted after 360 min to afford $(S_{ax}SS)$-**3** in high purity (> 99 %). The epimerization process can be stopped at any arbitrary ratio by cooling to room temperature.

^{31}P{^{1}H} NMR spectroscopy to follow the shift of the diastereomeric ratio (Figure 3).

Indeed, a reversal of the diastereomeric ratio is achieved at 70 °C within 100 min and complete de-epimerization within 360 min, which suggests a bidirectional enantioselectivity solely controlled by temperature. The epimerization process, which follows a sigmoidal function (Figure 3), can be stopped at any arbitrary ratio, here at ratios of 58:42, 45:55, 26:74, 14:86, 12:88, and < 1:99 for $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3**, by cooling to room temperature. Shifting the diastereomeric ratio back to the initial 61:39 ratio would require de-complexation, ligand re-equilibration, and re-complexation, because the diastereomerically pure catalyst remains at a ratio of < 1:99 upon cooling.

We comprehensively studied several diastereomeric ratios of the 3,3′-BIPHEP^{ONap}*Rh^I catalyst $(R_{ax}SS)$-**3** and $(S_{ax}SS)$-**3** in the asymmetric hydrogenation of (*Z*)-methyl-α-acetamidocinnamate (MAC, **4a**) as a prochiral substrate (Figure 4). The reactions were performed at temperatures between −40 and −10 °C and under an initial hydrogen pressure of 10 atm at different $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3** catalyst ratios by utilizing high-pressure tube autoclaves. These reactors are charged with NMR tubes as an inert reaction inlet to directly determine the stereoisomeric ratio and detect potential epimerization of the diastereomeric catalysts by comparing NMR measurements before and after catalysis. The conversion of the substrate was measured by NMR spectroscopy, and the absolute configurations and the enantiomeric ratio of the hydrogenation products *N*-acetylphenylalanine methyl ester (**5a**) were determined by HPLC by comparison to known standards directly after each catalytic run. To ascertain the upper and lower limits of the catalyst's enantioselectivity, we also determined the enantiomeric ratios e.r. in the hydrogenation catalysis by using the Rh^I complexes of the ligand isomers, which were separated by preparative HPLC on a chiral stationary phase. For these stereoisomerically pure catalysts we obtained enantiomeric ratios of the *N*-acetylphenylalanine methyl ester (**5a**) of 98:2 ((*R*)-**5a**/(*S*)-**5a**, 96 % *ee*) with $(R_{ax}SS)$-**3** and 2:98 ((*R*)-**5a**/(*S*)-**5a**, 96 % *ee*) with $(S_{ax}SS)$-**3**. This is a remarkable result, since diastereomeric complexes typically exhibit matched or mismatched behavior and therefore the enantioselectivity is decreased for one of the product enantiomers.

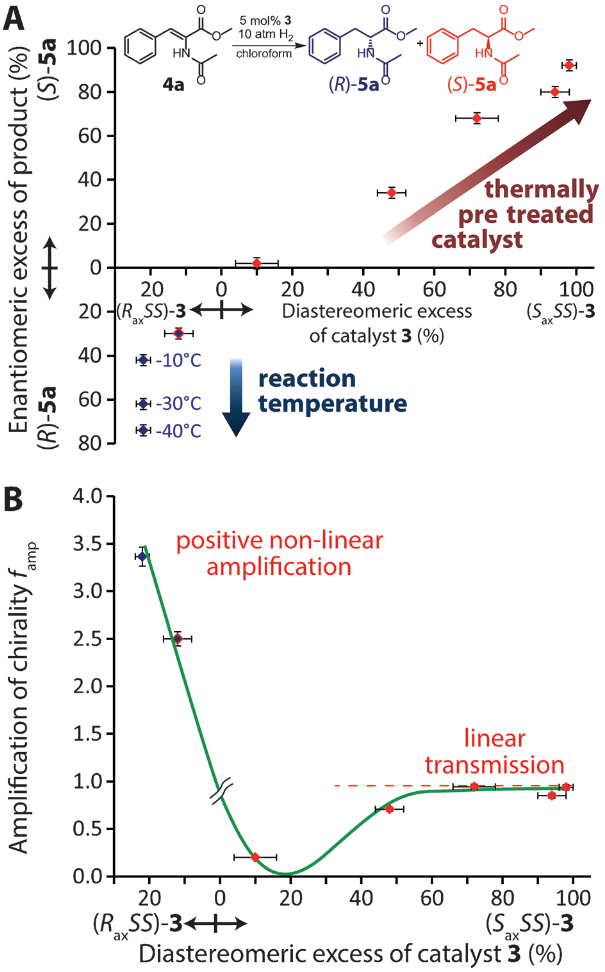
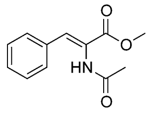
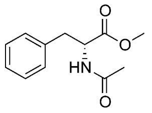
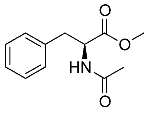
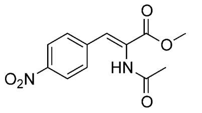
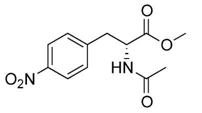
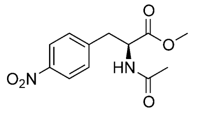
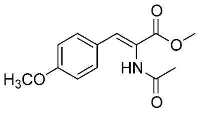
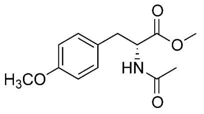
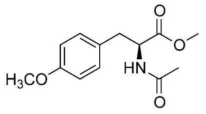
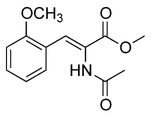
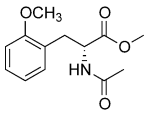
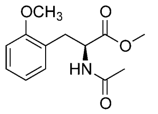
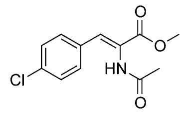
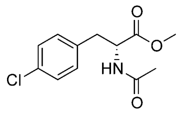
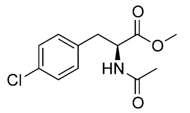
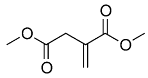
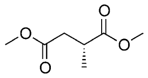
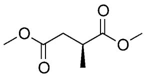
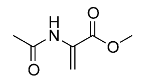
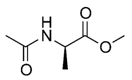
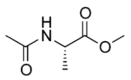


Figure 4. Enantioselectivity and amplification of chirality of Rh^I catalyst **3** in the asymmetric hydrogenation of (*Z*)-methyl-α-acetamidocinnamate (**4a**) to *N*-acetylphenylalanine methyl ester (**5a**) depending on the diastereomeric excess of the 3,3′-BIPHEP^{ONap}*Rh^I catalysts **3**. A) Blue data points: the *R* product is formed predominately by catalyst $(R_{ax}SS)$-**3**. Lowering the reaction temperature to −40 °C at a catalyst ratio $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3** of 61:39 leads to an additional increase of the enantiomeric excess from 42 % to 74 %. Red data points: Thermally pretreated catalyst leading to altered catalyst ratios $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3**. A catalyst ratio $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3** greater than 45:55 leads to a reversal of the enantioselectivity, with predominantly the *S* product produced. Reaction temperature: −10 °C. B) Corresponding plot of the maximum amplification of chirality achieved in the catalytic hydrogenation depending on the diastereomeric ratio of catalyst **3**.

Next, we investigated the catalysts with the frozen original isomer ratio of 61:39 $(R_{ax}SS)$-**3**/$(S_{ax}SS)$-**3** in the same asymmetric hydrogenation reaction. At −10 °C we observed a slight nonlinear amplification of the enantiomeric ratio of 71:29 ((*R*)-**5a**/(*S*)-**5a**) instead of the expected maximum enantiomeric ratio of 61:39 (*R*/*S*; Figure 4 A, blue data points). This corresponds to an amplification factor f_{amp} of 1.9. The amplification factor f_{amp} is defined as the ratio of the enantiomeric excess of the reaction product and the diastereomeric excess of the 3,3′-BIPHEP^{ONap}*Rh^{I} catalyst ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** ($f_{amp} = ee_{prod}/de_{cat}$). Investigation of this nonlinear chiral amplification at lower reaction temperatures (−30 °C and −40°), which did not change the isomeric ratio of the catalyst **3**, confirmed that ($R_{ax}SS$)-**3** catalyzes the kinetically favored formation of (*R*)-*N*-acetylphenylalanine methyl ester ((*R*)-**5a**). By decreasing the reaction temperature to −40 °C, the enantiomeric ratio even increased to 87:13 ((*R*)-**5a**/((*S*)-**5a**; Figure 4A). Kinetic evaluation of these data yields an acceleration of 4.3 for the kinetically favored reaction and a difference in enantioselectivities $\Delta\Delta H^{\ddagger}$ of 18.4 kJ mol^{-1} and $\Delta\Delta S^{\ddagger}$ of 67 J K^{-1} mol^{-1} between the 3,3′-BIPHEP^{ONap}*Rh^{I} catalysts ($R_{ax}SS$)-**3** and ($S_{ax}SS$)-**3**. This is a significant result in terms of the mechanism of chiral amplification since it proves that even small deviations from a 1:1 equilibrium are sufficient to generate high selectivity just by varying the external conditions, such as the reaction temperature.

Table 1: Enantioselectivity of the bidirectional Rh^{I} catalyst **3** in the asymmetric hydrogenation of (*Z*)-methyl-α-acetamidocinnamate derivatives, dimethyl itaconate (**6**), and methyl-α-acetamidoacrylate (**8**).[a]

Substrate	*R* Product	*S* Product	Product enantiomeric ratio *R*/*S* [%] catalyst ratio ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3**	
			61:39	<1:99
 **4a**	 (*R*)-**5a**	 (*S*)-**5a**	87:13	4:96
 **4b**	 (*R*)-**5b**	 (*S*)-**5b**	80:20	3:97
 **4c**	 (*R*)-**5c**	 (*S*)-**5c**	79:21	10:90
 **4d**	 (*R*)-**5d**	 (*S*)-**5d**	81:19	5:95
 **4e**	 (*R*)-**5e**	 (*S*)-**5e**	75:25	6:94
 **6**	 (*R*)-**7**	 (*S*)-**7**	20:80	98:2
 **8**	 (*R*)-**9**	 (*S*)-**9**	82:18	1:99 <1:99 (*S*)[b]

[a] Reaction conditions: 0.1 mmol substrate, 5 mol% **3** or 2 mol% **3** for dimethyl itaconate (**6**) and methyl-α-acetamidoacrylate (**8**), 10 atm hydrogen in chloroform. The absolute configurations of the hydrogenation products were obtained by chiral HPLC or GC by comparison to known standards. [b] Scale-up: 1.15 mmol **8**, 2.51 μmol **3** (0.2 mol%), 5 atm hydrogen, TON > 460.

3,3′-BIPHEP^{ONap}*Rh^{I} catalyst mixtures ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** with ratios of 58:42, 45:55, 26:74, 14:86, 12:88, and < 1:99 were studied in the asymmetric hydrogenation of (*Z*)-methyl-α-acetamidocinnamate (**4a**, Figure 4). All the diastereomeric catalyst mixtures were highly active and converted the substrate into (*S*)-*N*-acetylphenylalanine methyl ester ((*S*)-**5a**) in enantiomeric excesses of up to 4:96 ((*R*)-**5a**/(*S*)-**5a**, 92% *ee*) for catalyst mixtures with a dominating ($S_{ax}SS$)-**3** epimer. This demonstrates that temperature-controlled bidirectional enantioselectivity in a stereodynamically flexible 3,3′-BIPHEP^{ONap}*Rh^{I} catalyst ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** is possible without any separation of the diastereomers. Amplification of the chirality[23,24] f_{amp} was plotted as a function of the diastereomeric excess of the catalyst (Figure 4B). A significant positive nonlinear effect of up to $f_{amp} = 3.4$ (at a diastereomeric excess of only 22% of the catalyst) in amplification of the enantioselectivity is observed for the 3,3′-BIPHEP^{ONap}*Rh^{I} catalyst ($R_{ax}SS$)-**3** (Figure 4B). It has to be noted that complete stereocontrol corresponds only to a linear transmission of the chirality, in which the amplification factor converges to 1.0, as is seen in the right branch of the plot depicted in Figure 4B. A detailed discussion of the origin and principle of nonlinear effects in catalysis using diastereomeric ligand mixtures has been reported in the literature, for example, for asymmetric dihydroxylation,[25] asymmetric additions of terminal alkynes,[26] and enantioselective Cu^{I}-catalyzed three-component reactions.[27] Nonlinear effects in asymmetric hydrogenations were observed in catalysts built from (mixed) pairs of monophosphorus ligands, for example, phosphonites, phosphites, and phosphoramidites.[28–31] The distinct kinetics of the hydrogenation of the cod spectator ligand from the two diastereomeric precatalysts can additionally contribute to the nonlinear effect.[32]

We extended the here-reported novel concept of bidirectional enantioselectivity to (*Z*)-methyl-α-acetamidocinnamate derivatives **4** bearing either electron-withdrawing or -donating substituents at the phenyl group, dimethyl itaconate (**6**), and methyl-α-acetamidoacrylate (**8**). Hydrogenations were performed first with the temperature-depleted $<$1:99 ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** catalyst mixture at −10 °C and second with the original 61:39 ($R_{ax}SS$)-**3**/($S_{ax}SS$)-**3** mixture at −40 °C (Table 1). In all cases, significant nonlinearities were observed, with the 61:39 catalyst mixture giving enantiomeric ratios of up to 87:13 (*R* product/*S* product) for the *N*-acetylphenylalanine methyl ester derivatives **5**, up to 20:80 (*R* product/*S* product) for dimethyl-2-methyl succinate (**7**), and up to 82:18 (*R* product/*S* product) for the *N*-acetylalanine methyl ester (**9**). The $>$99 % ($S_{ax}SS$)-**3** catalyst was found to be highly enantioselective for the opposite enantiomer in all cases, thereby leading to enantiomeric ratios of up to 3:97 (*R* product/*S* product) for the *N*-acetylphenylalanine methyl ester derivatives **5**, up to 98:2 (*R* product/*S* product) for dimethyl-2-methylsuccinate (**7**), and up to 1:99 (*R* product/*S* product) for the *N*-acetylalanine methyl ester (**9**). Scale up of the asymmetric hydrogenation of methyl-α-acetamidoacrylate (**8**) at a low catalyst loading of only 0.2 mol % yielded (*S*)-*N*-acetylalanine methyl ester ((*S*)-**9**) with an enantiomeric ratio of 1: $>$99 (*R* product/*S* product) and a turnover number (TON) of $>$460.

In summary, we demonstrated the first example of an easily accessible catalytic system that provides access to both enantiomers of an asymmetric hydrogenation reaction solely by changing the applied temperature. Key features are the stereolabile tropos ligand core in combination with a remotely bound auxiliary. Synergy of highly selective asymmetric deactivation, nonlinearity, and stereodynamics result in a catalytic system that provides high enantioselectivities in both directions depending on the applied temperature. This bidirectional 3,3′-BIPHEP$^{\mathrm{ONap}}$*Rh$^{\mathrm{I}}$ catalyst shows excellent results in asymmetric hydrogenations to yield D- and L-phenylalanine derivatives, which are pharmaceutically relevant, for example, in the Parkinson's drug L-DOPA, dimethyl-2-methylsuccinate, and *N*-acetylalanine methyl ester. We assume that the underlying fundamental principle of this concept is directly transferable to other catalyzed reactions. The here-presented approach allows decoupling kinetic and thermodynamic control according to the Curtin–Hammett principle of enantiomeric catalysts (Figure S2). The discovery of temperature-controlled bidirectional enantioselectivity and chiral amplification as demonstrated herein is not only interesting in asymmetric synthesis but could be a key mechanism to trigger homochirality by temperature gradients, as was identified in the (spontaneous) polymerization of RNA.[33]

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[34] CCDC 1043639 [(R_{ax})-**1**] and CCDC 1043640 [($S_{\text{ax}}SS$)-**2**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.