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Combination of Enantioselective Metal Catalysis and Organocatalysis: Enantioselective Sequential Hydroformylation/Aldol Reactions

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Abstract: This work reports the possibility of controlling the sense of enantio- and diastereoinductions in the sequential hydroformylation and aldol reactions *via* the judicious combination of a chiral metal catalyst with a chiral organocatalyst. The diastereoselectivity of the reaction between styrene, syngas and acetone can be increased by using a *matched* pair of catalysts, [rhodium/(2*S*,4*S*)-Chiraphite]/(*S*)-organocatalyst and decreased, but not inverted, by using a *mismatched* pair of catalysts, [rhodium/(2*R*,4*R*)-Chiraphite]/(*S*)-organocatalyst.

Keywords: aldol reaction; asymmetric catalysis; hydroformylation; organocatalysis; tandem reactions

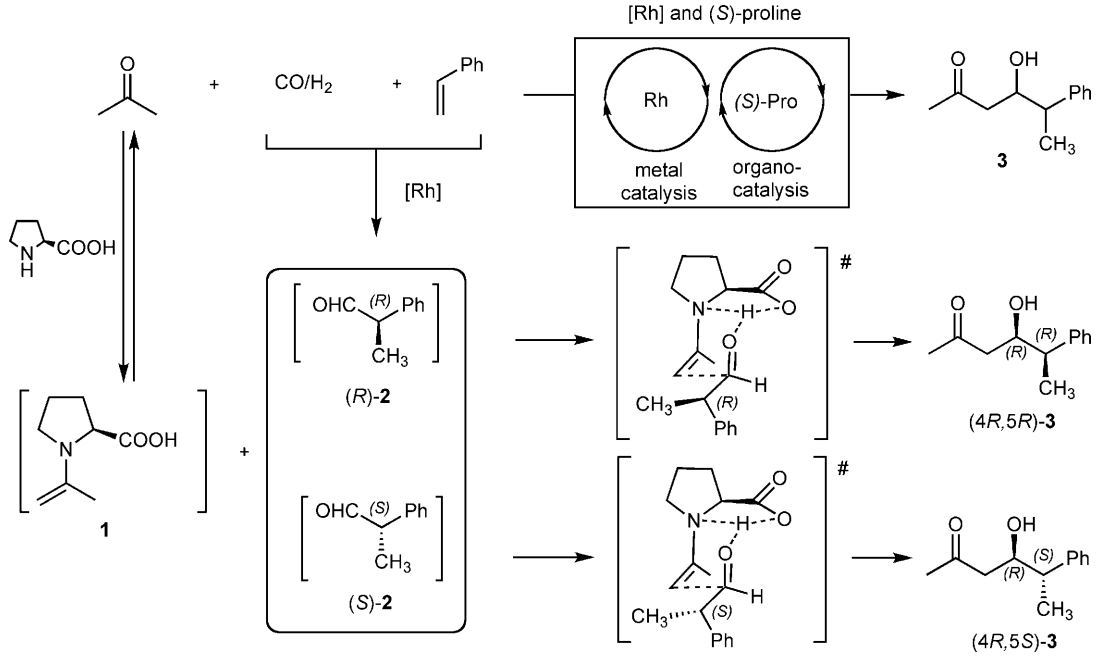
In order to achieve the highest possible efficiency in enantioselective chemical transformations, the number of steps must be kept to a minimum and the yield, regio-, enantio- and diastereoselectivities of each step should approach 100%. To meet this enormous challenge, several reactions can be combined in tandem reaction sequences.[1] Moreover, multiple chiral catalysts operating simultaneously could circumvent the time and yield losses associated with the isolation and purification of stereoisomers in multistep sequences.

In contrast to the major progress made in asymmetric multicatalysis using multimetallic,[2] multiorganocatalytic[3] or metal-enzyme systems,[4] very few reports exist on the combination of metal with organocatalysts to accomplish an asymmetric reaction.[5] Recently, achiral metal catalyst/chiral organocatalyst[6] and chiral metal catalyst/achiral organocatalyst catalytic systems have been reported.[7] However, a methodology where the absolute configuration of one stereogenic center in the product is controlled by a chiral metal-ligand complex and the configuration of another stereogenic center is controlled by a chiral organocatalyst has not been very successful so far.[6g] Considering the multitude of enantioselective reactions catalyzed by either metal catalysts (reductions, oxidations, σ-bond insertions, π-bond activation, Lewis acid reactions)[8] or organocatalysts (enamine, iminium, hydrogen-bonding, SOMO, counter ion catalysis)[9] we envision a tremendous potential for the creation of unique multicatalytic systems to influence chirality in reaction products.

In this report we present the combination of a chiral rhodium catalyst with a chiral organocatalyst in an enantioselective sequential hydroformylation followed by an aldol reaction (Scheme 1).

The sequential conversion of styrene with syngas and acetone to aldol product **3** was chosen as a model reaction. We presumed that exposure of styrene to a chiral Rh catalyst under hydroformylation conditions would generate an enantioenriched aldehyde **2**, which can be intercepted in the second catalytic cycle by the chiral enamine derived from acetone and (*S*)-proline. We envisioned that control of the sense of enantio- and diastereoinductions (e.g., *S vs. R*, *anti vs. syn*) could be achieved *via* judicious selection of the chiral catalysts involved in each catalytic cycle. The synthetic plan relied on finding optimal conditions for both enantioselective hydroformylation and enantioselective aldol reactions and then combining these reactions into a tandem sequence.

Our starting point was the Rh-catalyzed enantioselective hydroformylation of styrene. Styrene was chosen as a substrate in order to avoid the regioselectivity problems of hydroformylation reactions. It is reported that Rh complexes modified with bidentate phosphorus ligands such as (*R*,*S*)-BINAPHOS[10] and (*R*,*S*)-YanPhos[11] give the best enantioselectivities and excellent regioselectivities in styrene hydroformylation. However, we did not consider them suitable



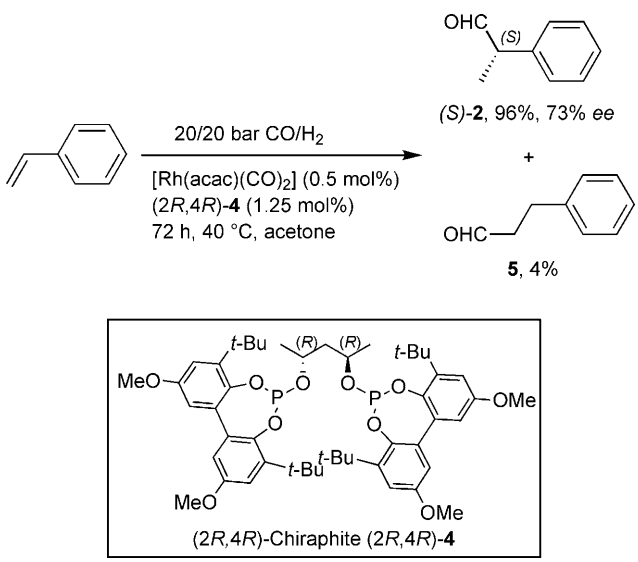
Scheme 1. Enantioselective sequential hydroformylation and aldol reactions.

for a tandem reaction, since they usually operate at temperatures higher than 60 °C.[12] Loss of steric information *via* formation of the α,β-unsaturated ketones in the subsequent aldol reaction at these temperatures might be a problem. In contrast, Rh catalysts modified with Chiraphite ligands **4** were reported to be used under relatively mild reaction conditions (25–40 °C, 9 bar of CO/H_2 1:1 pressure, toluene) achieving good enantioselectivities (up to 76%) at reasonable conversion (50%).[13]

First, the [Rh/(2*R*,4*R*)-Chiraphite]-catalyzed enantioselective hydroformylation of styrene was adapted to be combined with an aldol reaction. The reaction was performed at 20/20 bar pressures of CO/H_2 (reported to be the optimal pressure for tandem hydroformylation and enantioselective aldol reactions)[6a] in acetone (in the subsequent aldol reaction acetone would serve both as the enamine component and as solvent) (Scheme 2).

According to GC analysis, styrene was fully consumed after 72 h at 40 °C. (*S*)-2-Phenylpropanal (*S*)-**2**[14] was obtained with excellent regioselectivity in 73% *ee* (Scheme 2). GC analysis revealed that during the enantioselective hydroformylation, racemization of the aldehyde by the Rh catalyst does not occur. With all these findings in hand we could now proceed to the organocatalyzed enantioselective aldol reaction (Table 1).

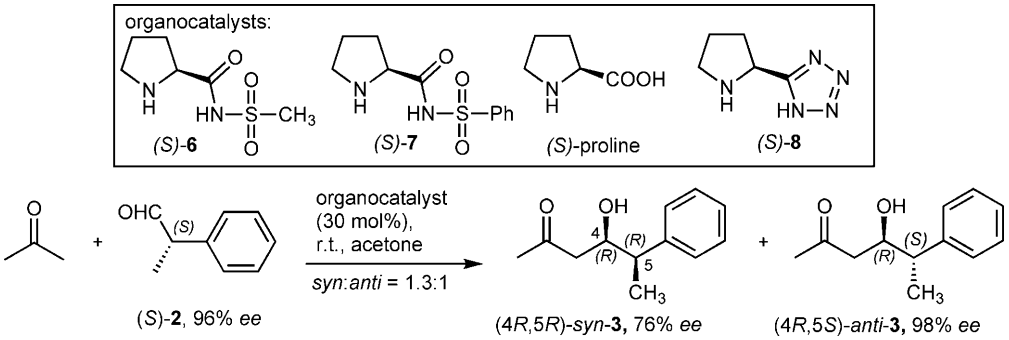
A range of organocatalysts was therefore tested in the reaction between (*S*)-2-phenylpropanal (96% *ee*) (*S*)-**2**[15] and acetone (Table 1). The catalytic efficiency of sulfonamides (*S*)-**6**[16] and (*S*)-**7**[16b,17] proved to be very low (Table 1, entries 1 and 2). In contrast, proline-tetrazole (*S*)-**8**[18] and (*S*)-proline[19] gave excellent aldehyde conversions within 7 h and 72 h, respectively (entries 3 and 5). The diastereomeric ratio and *ee* of the aldol products[20] (*syn/anti* = 1.3:1, with 76% and 98% *ee*, respectively) proved to be identical for all conversions independent of the type of the catalyst used.



Scheme 2. Enantioselective hydroformylation of styrene.

These results are not only interesting with respect to the different activities and identical selectivities of the organocatalysts chosen, but also informative if looking at the stereochemical outcome. Starting with 98% of the (*S*)-aldehyde **2** [96% *ee*, *vs.* 2% of the

Table 1. Enantioselective organocatalyzed aldol reactions.



Entry	Catalyst	Time [h]	Conversion [%][a]	**3** [%][b]
1	(*S*)-**6**	72	55	10
2	(*S*)-**7**	72	60	12
3	(*S*)-proline	72	96	87
4	(*S*)-proline	7	38	25
5	(*S*)-**8**[c]	7	98	88

[a] Determined by GC using dodecane as an internal standard.
[b] Isolated yield.
[c] 5 mol% of catalyst was used.

(*R*)-configuration] the isolated aldol products have a total of 50% of the former (*S*)-configuration and 50% of the (*R*)-configuration in the 5-position (stemming from the aldehyde).[21] Thus the (*S*)-aldehyde must have been racemized under the reaction conditions to preferentially form the (4*R*,5*R*)-*syn*-aldol product (>49%), and only traces of the (4*S*,5*R*)-*anti*-aldol product (<1%). Obviously, in the conversion of the (*R*)-aldehyde with acetone and the (*S*)-proline organocatalyst to the *syn*-aldol product both chiral units are directing towards the (4*R*)-configuration in the aldol product, thus representing the *matched* case of a double stereodifferentiation.[21] Conversion of the (*S*)-aldehyde with (*S*)-proline preferably leading to (*4R,5S*)-*anti*-aldol product (43%) is accompanied by 7% of the (*4S,5S*)-diastereoisomer.[21] This is obviously representing the *mismatched* case with (*S*)-proline overriding the opposite directing effect of the chiral centre in the aldehyde. Thus racemization of the starting (*S*)-aldehyde must play an important role under the conditions of this organocatalyzed cross-aldol reaction.

Indeed, with GC monitoring we observed that all four organocatalysts racemize aldehyde (*S*)-**2** at similar rates. For a better understanding of this phenomenon we performed control experiments of proline-catalyzed racemization of the aldehyde (*S*)-**2** (96% *ee*) in different solvents (dichloromethane, 3-pentanone and cyclohexanone) (Figure 1).

3-Pentanone and cyclohexanone were chosen as solvents because they are similar to acetone but do not react with (*S*)-**2** in the presence of proline. In these acetone-like solvents both proline enantiomers slowly racemize aldehyde (*S*)-**2** at similar rates. A drop in *ee* from 96% to 75–83% was observed after 5 h (Figure 1). In contrast, with dichloromethane as the solvent relatively fast aldehyde racemization was observed. Here, after 5 h the aldehyde was almost completely racemized. In addition we investigated which part of the organocatalyst is responsible for the racemization. Here, we found very fast racemization (<2 min) in the presence of pyrrolidine and no racemization in the presence of acetic acid. These results can be interpreted as an aldehyde deprotonation or the formation of the corresponding enamine from pyrrolidine.

We presumed that in a sequential hydroformylation/aldol reaction it would be possible to adjust the hydroformylation and racemization rates relative to

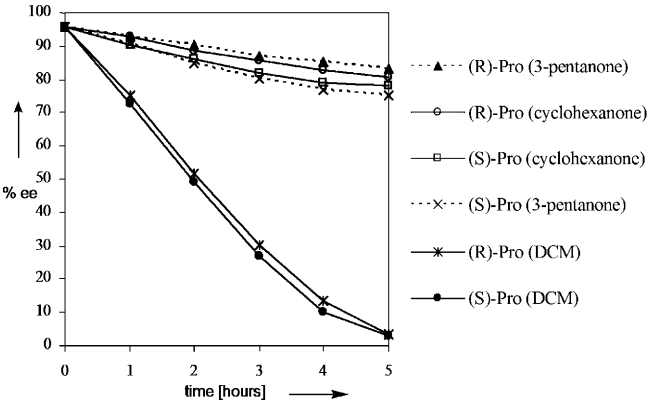


Figure 1. Proline-catalyzed racemization of (*S*)-2-phenylpropanal (*S*)-**2** in different solvents.

the aldol addition rate in such a way as to increase the aldol reaction rate and minimize accumulation of the aldehyde during the reaction. Thus, keeping the stationary concentration of the aldehyde at a low level should minimize the contact of the aldehyde with the organocatalyst and consequently lead to suppression of the undesired racemization.

In order to confirm this hypothesis, tandem reactions of chiral rhodium complex-catalyzed hydroformylation and organocatalyzed aldol addition (both catalysts present from the beginning of the reaction) and one-pot versions (the organocatalyst is added after enantioselective hydroformylation is completed) were carried out starting from styrene as the substrate and acetone as a substrate and also as a solvent (Table 2).

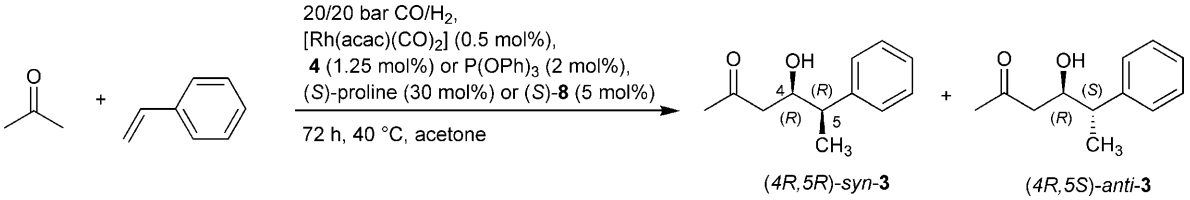
When using the best organocatalysts, as shown in Table 2, the yields of the aldol product **3** were good (63–83%). It is important to note that the presence of the organocatalysts affects the rate of enantioselective hydroformylation in this tandem reaction. Thus styrene is not fully converted after 72 h (entries 3, 4, 6 and 7). Analysis of the results assembled in Table 2 indicate that the stereoselectivities of the sequential reactions are controlled by a complex series of factors amongst which are the rates of enantioselective hydroformylation, aldehyde racemization and double stereodifferentiation in the aldol addition. In an ideal tandem reaction, the aldol reaction should have much higher rates than aldehyde racemization.

A combination of achiral $P(OPh)_3$-modified Rh catalyst with an (*S*)-organocatalyst affords low *syn/anti*-diastereoselectivities (1.8:1 in favour of the *syn* product, Table 2, entries 1 and 2). When a chiral Rh catalyst is combined with an (*S*)-organocatalyst, a *two-fold asymmetric induction* is expected.[22] This means that the stereoselectivity of the aldol addition step is not only controlled by the configuration of the organocatalyst, but also by the aldehyde configuration formed *via* enantioselective hydroformylation.

In the *mismatched* case mediated by a *mismatched* pair of catalysts, [Rh/(2*R*,4*R*)-**4**] [preferentially leading to the (*S*)-aldehyde] and (*S*)-organocatalyst [directing towards the (4*R*)-configuration in the aldol product], formation of the *anti* isomer (4*R*,5*S*)-**3** should be enhanced. Indeed, with the chiral Rh catalyst the diastereoselectivity is lowered (1.3:1 *dr* in favour of *syn,* entries 3, 4 and 5) as compared with the achiral rhodium catalyst (entries 1 and 2), but it is not reversed. Despite the fact that the enantioselectivity for the *anti* product is very high (98% *ee*), the major product is the *syn* isomer (4*R*,5*R*)-**3** with 76% *ee*.

In contrast, with a combination of the [Rh/(2*S*,4*S*)-**4**] and an (*S*)-organocatalyst much higher diastereo- and enantioselectivities for aldol product (4*R*,5*R*)-*syn*-**3** are observed. The selectivities in favour of (4*R*,5*R*)-*syn*-**3** could be improved from 3:1 *dr* (84% *ee*) to 6.6:1 *dr* (93% *ee*) by changing (*S*)-proline to (*S*)-**8** and from tandem reaction to one-pot version

Table 2. Enantioselective sequential hydroformylation and aldol reactions.



Entry	Type of reaction[a]	Ligand	Organocatalyst	Styrene conversion [%][b]	**3** [%][c]	*syn*:*anti*[d]	*ee* **3** [%][e] 4*R*,5*R*	4*R*,5*S*
1[6a]	Tandem	$P(OPh)_3$	(*S*)-proline	>99	83	1.8:1	72	>99
2	Tandem	$P(OPh)_3$	(*S*)-**8**	>99	83	1.8:1	72	>99
3	Tandem (*mismatched*)	(2*R*,4*R*)-**4**	(*S*)-proline	87	64	1.3:1	76	98
4	Tandem (*mismatched*)	(2*R*,4*R*)-**4**	(*S*)-**8**	84	63	1.3:1	76	98
5	One-pot (*mismatched*)	(2*R*,4*R*)-**4**	(*S*)-**8**	>99	68	1.3:1	76	98
6	Tandem (*matched*)	(2*S*,4*S*)-**4**	(*S*)-proline	88	65	3:1	84	80
7	Tandem (*matched*)	(2*S*,4*S*)-**4**	(*S*)-**8**	87	64	4:1	83	49
8	One-pot (*matched*)	(2*S*,4*S*)-**4**	(*S*)-**8**	>99	69	6.6:1	93	69

[a] Tandem = chiral metal catalyst and chiral organocatalyst are present from the beginning of the reaction; one-pot = chiral organocatalyst is added after hydroformylation is completed and the reaction mixture is stirred at room temperature and atmospheric pressure for an additional 16 h.
[b] Determined by GC using dodecane as an internal standard.
[c] Isolated yield.
[d] Determined by ^{1}H NMR analyses.
[e] Determined by chiral HPLC.

(entries 6, 7 and 8). This can be attributed to a *matched* case of *double stereodifferentiation* establishing a strong improvement in stereoselectivity, especially if considering the fact that the *ee* of the aldehyde obtained in the hydroformylation step cannot exceed 73% (Scheme 2).

Moreover, in entry 8, the calculated ratio of the carbon stereocenters bearing the *Ph* group [(5*S*)/(5*R*) = 86:14][21] is very similar to that from the (*S*)-aldehyde obtained in enantioselective hydroformylation [(*S*)/(*R*) = 86.5:13.5][21] from Scheme 2. This means that in the one-pot reaction, for the *matched* case, racemization of the aldehyde during the aldol reaction is almost completely suppressed. From these results, we conclude that, in contrast to our initial presumption, keeping the stationary concentration of aldehyde at a low level has a smaller effect on asymmetric induction during the subsequent aldol addition step, as compared with the one-pot version. In the *mismatched* case, however, the ratio (5*S*)/(5*R*) = 50:50[21] (entries 4, 5 and 6). This implies that aldehyde racemization during the aldol addition here has a greater impact on the asymmetric induction (see Figure 1).

In conclusion, the work reported here shows that it is possible to control the sense of enantio- and diastereoinductions in sequential hydroformylation and aldol reactions *via* the judicious combination of a chiral metal catalyst with a chiral organocatalyst under suitable reaction conditions. The diastereoselectivity of the reaction between styrene, syngas and acetone can be considerably increased by using a *matched* pair of catalysts [Rh/(2*S*,4*S*)-Chiraphite]/(*S*)-organocatalyst and decreased, but not inverted, by using a *mismatched* pair of catalysts [Rh/(2*R*,4*R*)-Chiraphite]/(*S*)-organocatalyst.

Moreover in the *matched* case the easily racemized aldehyde obtained after the hydroformylation step is converted to an aldol product without loss of its chiral information.

The cooperation of chiral metal catalysts and chiral organocatalysts offers many other possibilities for asymmetric transformations. This approach is likely to lead to the development of powerful methods for the generation of complex optically active molecules from simple starting materials.

Experimental Section

General Remarks

Enantioselective hydroformylation and tandem reaction experiments were carried out in a BERGHOF HR-200 high-pressure reactor with magnetic stirring and electrical heating. The inside part of the cover was made from Teflon® to protect the solution from direct contact with the stainless steel. Commercial reagents were used as received. (2*R*,4*R*)-Chiraphite,[13a] (2*S*,4*S*)-Chiraphite,[13a] (*S*)-**6**,[18e] (*S*)-**7**[18e] and (*S*)-**8**[18e] were synthesized according to the literature procedures. Column chromatography was carried out using MN Kieselgel 60 (0.063–0.2 mm/70–230 mesh). TLC was performed on Merck Silica gel 60 F254 plates. Visualization of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or by anisaldehyde stain. For gas chromatographic analyses, a Carlo Erba HRGC Mega2 Series MFC 800 chromatograph with a Carlo Erba EL 580 flame-ionization detector (FID) was used. Separations were performed on the Supelco Beta Dex 225 column. Semi-preparative HPLC was performed using a SUPELCOSIL™ LC-SI 5 μm (25 cm × 21.2 mm) column. Analytical HPLC was performed on a Hewlett–Packard 1050 Series chromatograph using CHIRALCEL OJ-H (250 × 4.6 mm) and CHRALPAK AD (250 × 4.6 mm) columns as noted.

Enantioselective Hydroformylation of Styrene (Scheme 2)

To a solution of [Rh(acac)(CO)$_2$] (1 mg, 0.0039 mmol, 0.005 equiv.) in 2 mL of acetone in a vial, was added (2*R*,4*R*)-Chiraphite (2*R*,4*R*)-**4** (9 mg, 0.0097 mmol, 0.0125 equiv.). The solution was stirred with magnetic stirrer for 5 min and then charged with styrene (81 mg, 0.78 mmol, 1 equiv.) and dodecane (40 mg, 0.234 mmol, 0.3 equiv.). The vial was transferred to the autoclave, pressurized with 20/20 bar CO/H$_2$ and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurized, flushed with argon and opened to obtain a sample for GC analysis. GC conditions: carrier gas 50 kPa He, temperature program of 100 °C for 5 min, then 4 °C/min to 160 °C and 20 °C/min to 200 °C; retention times: 8.69 min for styrene, 16.26 min for dodecane, 18.02 min for (*R*)-2-phenylpropanal, 18.28 min for (*S*)-2-phenylpropanal and 21.8 min for 3-phenylpropanal, in accord with the literature data.[14]

Enantioselective Organocatalyzed Aldol Reactions (Table 1)

To a stirred suspension of (*S*)-organocatalyst (0.3 mmol, 0.3 equiv.) in 5 mL of acetone was added dodecane (51 mg, 0.3 mmol, 0.3 equiv.) and (*S*)-2-phenylpropanal (134 mg, 1 mmol, 1 equiv.). The resulting mixture was stirred at room temperature until the reaction was completed. Then, the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography (EtOAc/cyclohexane 1:4) to afford the mixture of *syn/anti* diastereomers of the compound **3** as a colourless oil. Diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane, 1:6).

Proline-Catalyzed Racemization of (*S*)-2-Phenylpropanal in Different Solvents (Figure 1)

To a solution of (*S*)-2-phenylpropanal (96% *ee*) (20 mg, 0.15 mmol) in 1 mL of solvent in a flask, was added proline (5 mg, 0.045 mmol). The suspension was stirred with a magnetic stirrer at room temperature. A sample for GC analysis was taken every hour and analyzed immediately.

Tandem Hydroformylation and Enantioselective Aldol Addition (Table 2, entries 1 and 2)

To a solution of $[Rh(acac)(CO)_2]$ (5 mg, 0.019 mmol, 0.005 equiv.) in 2 mL of acetone in a vial, was added triphenyl phosphite (24 mg, 0.078 mmol, 0.02 equiv.). The solution was stirred with a magnetic stirrer for 5 min and then charged with styrene (395 mg, 3.8 mmol, 1 equiv.), dodecane (199 mg, 1.17 mmol, 0.3 equiv.) and (*S*)-organocatalyst (1.17 mmol, 0.3 equiv.). The vial was transferred to the autoclave, pressurized with 20/20 bar CO/H_2 and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurized, flushed with argon and opened to obtain a sample for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography (EtOAc/cyclohexane 1:4) to afford the mixture of *syn/anti* diastereomers of the compound **3** as a colourless oil. Diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane, 1:6) and analyzed by chiral HPLC.

Tandem Enantioselective Hydroformylation and Aldol Addition (Table 2, entries 3, 4, 6 and 5)

To a solution of $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol, 0.005 equiv.) in 2 mL of acetone in a vial, was added **4** (9 mg, 0.0097 mmol, 0.0125 equiv.). The solution was stirred with a magnetic stirrer for 5 min and then charged with styrene (81 mg, 0.78 mmol, 1 equiv.), dodecane (40 mg, 0.234 mmol, 0.3 equiv.) and organocatalyst (0.234 mmol, 0.3 equiv.). The vial was transferred to the autoclave, pressurized with 20/20 bar CO/H_2 and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurized, flushed with argon and opened to obtain a sample for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography (EtOAc/cyclohexane 1:4) to afford the mixture of *syn/anti* diastereomers of the compound **3** as a colourless oil. Diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane, 1:6) and analyzed by chiral HPLC.

One-Pot Enantioselective Hydroformylation and Aldol Addition (Table 2, entries 5 and 8)

To a solution of $[Rh(acac)(CO)_2]$ (1 mg, 0.0039 mmol) in 2 mL of acetone in a vial, was added **4** (9 mg, 0.0097 mmol, 0.0125 equiv.). The solution was stirred with a magnetic stirrer for 5 min and then charged with styrene (81 mg, 0.78 mmol, 1 equiv.) and dodecane (40 mg, 0.234 mmol, 0.3 equiv.). The vial was transferred to the autoclave, pressurized with 20/20 bar CO/H_2 and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurized, flushed with argon and opened to obtain a sample for GC analysis. Then organocatalyst (0.234 mmol, 0.3 equiv.) was added to the vial and the reaction mixture was stirred for an additional 18 h at room temperature and atmospheric pressure. After that the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated under vacuum and the crude product was purified by column chromatography (EtOAc/cyclohexane 1:4) to afford the mixture of *syn/anti* diastereomers of the compound **3** as a colourless oil. Diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane, 1:6) and analyzed by chiral HPLC.

(4*R*,5*R*)-4-Hydroxy-5-phenylhexan-2-one (Table 2, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.32$- 7.29 (m, 2H), 7.24–7.16 (m, 3H), 4.09 (ddd, 1H, $J = 7.9$, 5.8, 5.8 Hz), 2.74 (qd, 1H, $J = 7.9$, 7.0 Hz), 2.42–2.40 (m, 2H), 2.07 (s, 3H), 1.36 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.6$, 30.7, 45.4, 47.9, 72.1, 126.6, 127.6, 128.6, 143.8, 210.1; HRMS (FAB+): *m/z* 193.1236, exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_2$): 193.1229; elemental analysis (%), calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.48, H 8.50; IR (film): $\nu_{max} = 3461$, 2965, 1708, 1493, 1452, 1361, 1164, 702 cm^{-1}; $[\alpha]_D^{20}$: +13.8 (*c* 1.23, *n*-heptane); HPLC (CHIRALPAK AD, *n*-heptane/*i*-PrOH, 98:2, 1.0 mL min^{-1}, 254 nm): *ee* = 72%, t_R [(4*R*,5*R*)-**3**] = 18.6 min; t_R [(4*S*,5*S*)-**3**] = 20.3 min. All the spectral and HPLC data are in accord with the literature data.[6a]

(4*R*,5*S*)-4-Hydroxy-5-phenylhexan-2-one (Table 2, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$–7.31 (m, 2H), 7.26–7.22 (m, 3H), 4.20 (ddd, 1H, $J = 9.3$, 6.1, 2.6 Hz), 2.82 (qd, $J = 7.0$, 6.1 Hz), 2.58 (dd, 1H, $J = 17.2$, 2.6 Hz), 2.47 (dd, 1H, $J = 17.2$, 9.3 Hz), 2.14 (s, 3H), 1.31 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 17.0$, 30.8, 45.0, 47.3, 71.7, 126.6, 128.1, 128.4, 142.8, 209.4; HRMS (FAB+): *m/z* 193.1236, exact mass calcd. for $[M+H]^+$ ($C_{12}H_{17}O_2$): 193.1229; elemental analysis (%), calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.62, H 8.60; IR (film): $\nu_{max} = 3461$, 2965, 1708, 1493, 1452, 1361, 1164, 702 cm^{-1}; $[\alpha]_D^{20}$: +32.7 (*c* 1.97, *n*-heptane); HPLC (CHIRALCEL OJ-H, *n*-heptane/*i*-PrOH, 90:10, 1.0 mL min^{-1}, 254 nm): *ee* = > 99%, t_R [(4*R*,5*S*)-**3**] = 16.5 min, t_R [(4*S*,5*R*)-**3***J* = 22.99 min. All the spectral and HPLC data are in accord with the literature data.[6a]

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References

[1] a) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; b) J.-M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; c) L. F. Tietze, G. Brasche, K. Gerike, *Domino reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; d) D. E. Fogg, E. N. Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365; e) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

[2] a) M. Shibasaki, Y. Yamamoto, *Multimetallic Catalysts in Organic Synthesis*, Wiley-VCH, Weinheim, **2004**;

b) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117; c) B. M. Choudary, N. S. Chowdari, S. Madhi, M. L. Kantam, *Angew. Chem.* **2001**, *113*, 4755; *Angew. Chem. Int. Ed.* **2001**, *40*, 4619; d) T. Nemoto, H. Kakei, V. Gnanadesikan, S. Tosaki, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14544; e) T. Shimada, K. Mukaide, A. Shinohara, J. W. Han, T. Hayashi, *J. Am. Chem. Soc.* **2002**, *124*, 1584.

[3] a) D. Enders, C. Grondal, M. Huttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) Y. Huang, A. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; c) M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem.* **2009**, *121*, 3754; *Angew. Chem. Int. Ed.* **2009**, *48*, 3699; d) D. B. Ramachary, R. Sakthidevi, *Org. Biomol. Chem.* **2008**, *6*, 2488.

[4] a) M.-J. Kim, Y. I. Chung, Y. K. Choi, H. K. Lee, D. Kim, J. Park, *J. Am. Chem. Soc.* **2003**, *125*, 11494; b) B. Martin-Matute, J.-E. Backvall, *Curr. Opin. Chem. Biol.* **2007**, *11*, 226; c) R. Stuermer, *Angew. Chem.* **1997**, *109*, 1221; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1173.

[5] For a recent review on combining transition metal catalysis and organocatalysis, see: Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745.

[6] a) S. Chercheja, P. Eilbracht, *Adv. Synth. Catal.* **2007**, *349*, 1897; b) S. Chercheja, T. Rothenbuecher, P. Eilbracht, *Adv. Synth. Catal.* **2009**, *351*, 339; c) O. Abillard, B. Breit, *Adv. Synth. Catal.* **2007**, *349*, 1891; d) P. Kukula, V. Matousek, T. Mallat, A. Baiker, *Chem. Eur. J.* **2008**, *14*, 2699; e) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; f) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 3329; g) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *J. Org. Chem.* **2002**, *67*, 7418; h) S. Mukherjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 11336; i) X. Xu, J. Zhou, L. Yang, W. Hu, *Chem. Commun.* **2008**, 6564; j) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; k) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796; l) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875.

[7] a) R. Lebeuf, K. Hirano, F. Glorius, *Org. Lett.* **2008**, *10*, 4243; b) F. Bihelovic, R. Matovic, B. Vulovic, R. N. Saicic, *Org. Lett.* **2007**, *9*, 5063.

[8] a) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, **2004**; b) V. Caprio, J. Williams, *Catalysis in Asymmetric Synthesis*, Wiley-Blackwell, **2009**.

[9] a) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; b) A. Berkessel, H. Groeger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; c) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**; d) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[10] K. Nozaki, N. Sakai, T. Nanno, T. Higashijima, S. Mano, T. Horiuchi, H. Takaya, *J. Am. Chem. Soc.* **1997**, *119*, 4413.

[11] Y. Yan, Z. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198.

[12] a) J. Klosin, C. R. Landis, *Acc. Chem. Res.* **2007**, *40*, 1251; b) B. Zhao, X. Peng, Z. Wang, C. Xia, K. Ding, *Chem. Eur. J.* **2008**, *14*, 7847; c) G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *J. Mol. Catal. A: Chemical* **2008**, *280*, 148.

[13] a) G. J. H. Buisman, E. J. Vos, P. C. J. Kamer, W. N. M. P. v. Leeuwen, *J. Chem. Soc. Dalton Trans.* **1995**, 409; b) J. E. Babin, G. T. Whiteker, *PCT Int. Appl.* WO 9303839, **1993**.

[14] The assignment of the absolute configuration of the (*S*)-2-phenylpropanal was previously reported, see: a) ref.[12]; b) additions and corrections: C. J. Cobley, J. Klosin, C. Qin, G. T. Whiteker, *Org. Lett.* **2005**, *7*, 1197; c) C. J. Cobley, J. Klosin, C. Qin, G. T. Whiteker, *Org. Lett.* **2004**, *6*, 3277.

[15] (*S*)-2-Phenylpropanal was synthesized cleanly from commercially available (*S*)-2-phenylpropanol according to the literature procedure: C. Botuha, M. Haddad, M. Larcheveque, *Tetrahedron: Asymmetry* **1998**, *9*, 1929. The aldehyde can be stored under argon in the fridge for several weeks without significant racemization.

[16] For (*S*)-**6**-catalyzed aldol reactions see: a) S. Hajra, A. K. Giri, *J. Org. Chem.* **2008**, *73*, 3935; b) X.-J. Wang, Y. Zhao, J.-T. Liu, *Org. Lett.* **2007**, *9*, 1343.

[17] For (*S*)-**7**-catalyzed aldol reactions see: a) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci, M. Spiga, *Tetrahedron Lett.* **2008**, *49*, 3037; b) F. Silva, M. Sawicki, V. Gouverneur, *Org. Lett.* **2006**, *8*, 5417.

[18] For (*S*)-**8**-catalyzed aldol reactions see: a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983; b) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570; c) J. T. Suri, D. B. Ramachary, C. F. Barbas, *Org. Lett.* **2005**, *7*, 1383; d) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831; e) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84.

[19] For (*S*)-proline-catalyzed aldol reactions see: a) F. Zhang, Y. Peng, Y. Gong, *Chirality* **2008**, *20*, 805; b) G. Kumaraswamy, B. Markondaiah, *Tetrahedron* **2008**, *64*, 5861; c) B. Y. C. Chen, *Tetrahedron Lett.* **2008**, *49*, 672.

[20] The assignment of the absolute and relative configuration of aldol products **3** were previously reported in ref.[5a]

[21] The ratios of the stereocenters bearing the *Ph* group are calculated from the *dr* and *ee* of aldol products. The Supporting Information contains the information presented in Table 1 and Table 2 in an alternative format; ratios of all four stereoisomers are provided to give a clearer picture of *double asymmetric induction* and racemization.

[22] For examples of double asymmetric induction in proline-catalyzed aldol reactions see: a) F. Calderón, E. G. Doyagüez, A. Fernández-Mayoralas *J. Org. Chem.* **2006**, *71*, 6258; b) B. Alcaide, P. Almendros, A. Luna, M. R. Torres, *J. Org. Chem.* **2006**, *71*, 4818; c) F. Calderón, E. G. Doyagüez, P. H.-Y. Cheong, A. Fernández-Mayoralas, K. N. Houk *J. Org. Chem.* **2008**, *73*, 7916.

