Catalyst Repurposing Sequential Catalysis by Harnessing Regenerated Prolinamide Organocatalysts as Transfer Hydrogenation Ligands

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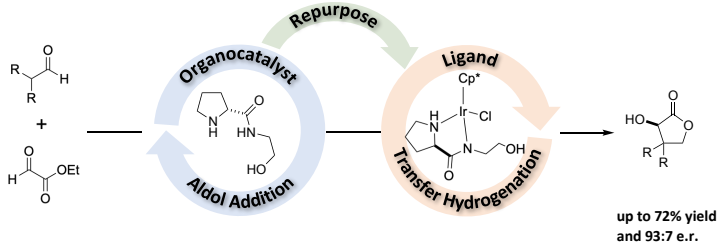
Supporting Information Placeholder

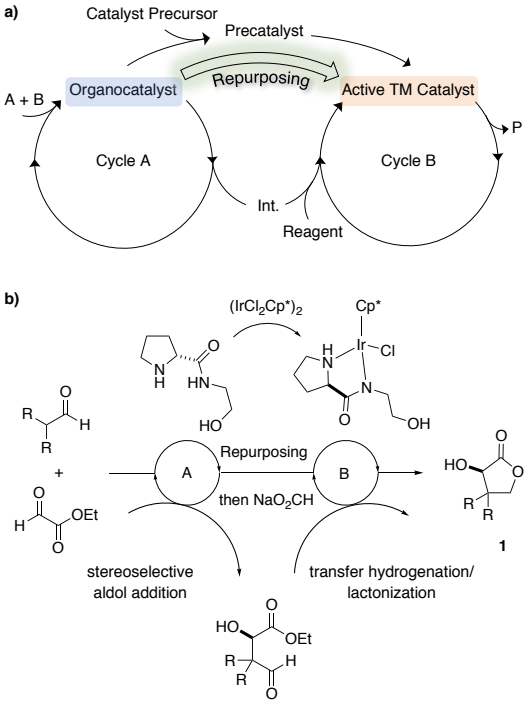
ABSTRACT: A catalyst repurposing strategy based on a sequential aldol addition and transfer hydrogenation giving access to enantiomerically enriched α-hydroxy-γ-butyrolactones is described. The combination of a stereoselective, organocatalytic step followed by an efficient catalytic aldehyde reduction induces an ensuing lactonization to provide enantioenriched butyrolactones from readily available starting materials. By capitalizing from the capacity of prolineamides to act both as organocatalyst and transfer hydrogenation ligand, catalyst repurposing allowed the development of an operationally simple, economic and efficient sequential catalysis approach.



- **Catalyst repurposing for sequential catalysis**
- **Stereoselective aldol addition/transfer hydrogenation/lactonization sequence**
- **Efficient and scalable synthesis of enantioenriched α-hydroxy-γ-butyrolactones**

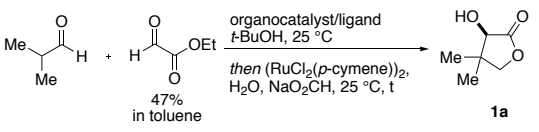
The combination of multiple distinct catalytic transformations in a one-pot reaction procedure enables cost- and time-efficient processes towards complex targets from readily available starting materials. Especially the interplay between organo- and transition metal catalysis can provide unique possibilities for the formation of valuable organic frameworks.[1] In relay, tandem or cascade catalysis, a common intermediate is released from the first catalytic cycle that directly enters a second one. This requires high reagent compatibility, which can often be circumvented by a sequential catalysis approach where after completion of the first catalytic event, reagents or catalysts required for the second transformation are added. This permits an increased scope and allows more variation of reaction conditions.[2] Since amines,[3] NHCs[4] and phosphines[5] are frequently used both as organocatalysts and ligands, we became intrigued by the prospects of a repurposing strategy where the first catalyst upon regeneration is converted into the second by the addition of a metal precatalyst (Scheme 1a). This in situ catalyst repurposing sequential catalysis strategy (CRSC) would thus constitute a particularly effective method for a wide range of transformations. We recognized prolineamides as an ideal compound class for CRSC as they have been successfully used as organocatalysts in stereoselective cross aldol reactions[6] and as ligands in transfer hydrogenations.[7] We hence envisioned to exploit the proline amide derivatives in CRSC for the stereoselective synthesis of α-hydroxy-γ-butyrolactones **1**, first as catalyst of a stereoselective aldol addition to intermediate **2** and after repurposing, as ligand to promote the aldehyde reduction which induces a lactonization (Scheme 1b).

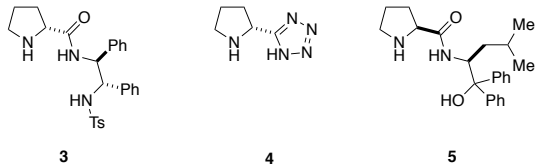
Scheme 1. Schematic Overview of Catalyst Repurposing Sequential Catalysis (CRSC)

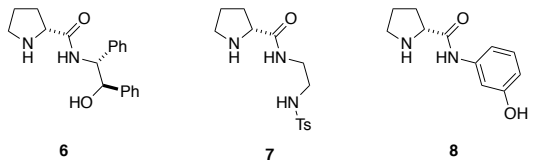


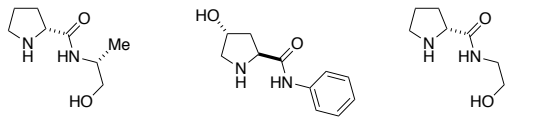
Enantioenriched α-hydroxy-γ-butyrolactones **1** are key industrial intermediates,[8] chiral auxiliaries[9] and building blocks for the synthesis of biologically active compounds and natural products.[10] Their previous preparation typically involved resolution protocols[8, 11] or a stepwise stereoselective catalysis strategy.[12] Interestingly, (*R*)-pantolactone **1a** (R=Me), the key intermediate for the synthesis of vitamin B_5 (pantothenic acid) was prepared by a one-pot combination of organo- and biocatalysts by Gröger, Berkessel and coworkers.[13] We thus initiated our catalyst repurposing study by preparing (*R*)-pantolactone **1a** using the regenerated amine catalyst as ligand for a transfer hydrogenation. To identify catalysts, solvents, additives and conditions suitable for both steps in the sequence, we first individually evaluated their effect on stereoselectivity and reactivity for the aldol addition and reduction (details of this prerequisite optimization are provided in the SI).

Table 1. Catalyst Repurposing Sequential Catalysis Design[a]









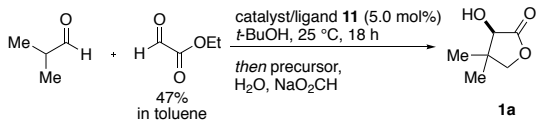
entry	catalyst/ ligand,	$(RuCl_2(p\text{-cymene}))_2$	t [h]	conv. [%][b]	e.r.
1	**3**, 10 mol%	2.5 mol%	18	99	82:18
2	**4,** 10 mol%	2.5 mol%	-	-	-
3	**5,** 10 mol%	2.5 mol%	-	-	-
4	**6,** 10 mol%	2.5 mol%	18	99	79:21
5	**7,** 10 mol%	2.5 mol%	18	99	85:15
6	**8,** 20 mol%	2.5 mol%	18	99	84:16
7	**9,** 10 mol%	1.0 mol%	18	99	85:15
8	**10,** 10 mol%	1.0 mol%	2	99	19:81
9	**11,** 5.0 mol%	1.0 mol%	4	**99**	**86:14**

[a] Reaction conditions: isobutanal (0.40 mmol), ethyl glyoxalate (0.40 mmol, 47 wt.% in toluene), organocatalyst (5.0 – 20 mol%), *t*-BuOH (0.4 mL), 25 °C, 24 – 48 h, TM precursor (1.0 – 2.5 mol%), sodium formate (2.00 mmol), water (1 mL), 25 °C, 2 – 18 h. [b] Conversion determined by GC analysis.

Intriguingly, initial results allowed to identify a hybrid between Noyori's TsDPEN ligand and D-proline (*R*)-**3** as suitable catalyst and ligand (Table 1)[14] and *t*-BuOH as compatible solvent. More specifically, upon completion of the enantioselective aldol addition after 24 hours, water, $(RuCl_2(p\text{-cymene}))_2$ and sodium formate (NaO_2CH) were added,[15-17] providing (*R*)-pantolactone after 18 h with a 99% conversion for both steps and an e.r. of 82:18. We next confirmed the requirement of the amide moiety by using pyrrolidinyl tetrazole (*R*)-**4**, which provided the expected unreduced aldol addition product. We further examined ethylene diamine or ethanolamine derivatives (*R*)-**5**–**7** and observed that also the hydroxy terminated (*R*)-**6** acts as suitable ligand for the transfer hydrogenation. With a 3-aminophenol derived catalyst (*R*)-**8**, the effect of the different amide residues on the rate of the aldol addition step was noticeable, requiring 20 mol% catalyst loading and prolonged reaction times. Structural simplification revealed, that also (*R*)-**9** is suitable for CRSC, even with a reduced $(RuCl_2(p\text{-cymene}))_2$ loading of 1.0 mol% (entry 7). Interestingly, (*S*)-**10** led to complete aldehyde reduction and lactonization within two hours at 25 °C and confirmed that a (*S*)-configured catalyst provides (*S*)-pantolactone. Intriguingly, the ethanolamine derived prolinamide (*R*)-**11**,[14b] which is readily available on large scale, provided (*R*)-pantolactone **1a** with a reduced catalyst/ligand loading of 5.0 mol% and 1.0 mol% $(RuCl_2(p\text{-cymene}))_2$ within four hours for the transfer hydrogenation step.

To further refine the CRSC, we next studied the effect of different transition metal precursors, their loading and the optimal temperature for the transfer hydrogenation step (Table 2).

Table 2. Effect of Transition-Metal Precursors[a]

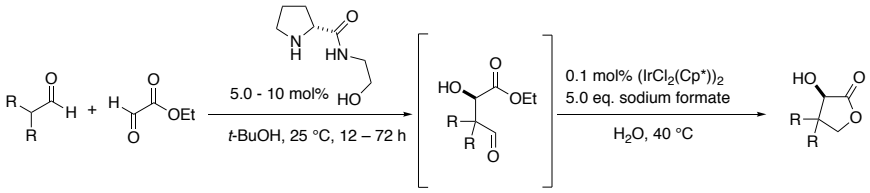


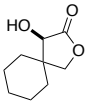
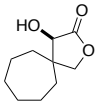
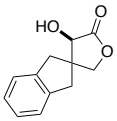
entry	precursor	precursor loading	T [°C]	t [h]	conv. [%][b]
1	$(RuCl_2(p\text{-cymene}))_2$	0.50 mol%	rt	26	98
2	$(RuCl_2(p\text{-cymene}))_2$	0.50 mol%	40	6	98[c]
3	$(RuCl_2(p\text{-cymene}))_2$	0.50 mol%	60	1	94
4	$(RuCl_2(\text{benzene}))_2$	0.50 mol%	40	5	92
5	$(RhCl_2Cp^*)_2$	0.50 mol%	40	2.5	97
6	$(IrCl_2Cp^*)_2$	0.50 mol%	40	1	99
7	$(IrCl_2Cp^*)_2$	0.50 mol%	rt	4	99
8	$(IrCl_2Cp^*)_2$	0.25 mol%	40	2	93
9	$(IrCl_2Cp^*)_2$	0.10 mol%	40	5	99

[a] Reaction conditions: isobutanal (0.40 mmol), ethyl glyoxalate (0.40 mmol, 47 wt.% in toluene), organocatalyst (5.0 mol%), *t*-BuOH (0.4 mL), 25 - 60 °C, 18 h, TM precursor (0.1 – 0.5 mol%), sodium formate (2.00 mmol), water (1 mL), 25 °C, 1 – 26 h. [b] Conversion determined by GC analysis. [c] scale-up to gram-scale (30 mmol) provides **1a** with 62% isolated yield and an e.r. of 86:14.

With a $(RuCl_2(p\text{-cymene}))_2$ precursor loading of 0.50 mol%, the aldehyde reduction required 26 hours to reach near completion, while increasing the temperature to 40°C allowed to reduce the reaction time to six hours. Satisfyingly, the catalyst-repurposing sequential catalytic reaction under these conditions was also readily applicable on gram-scale (30 mmol) providing (*R*)-pantolactone (**1a**) in an overall 62% yield and an enantiomeric excess of 86:14 (see SI for details). The reaction time could be further decreased to 1 h at 60 °C and a slight increase in reactivity was observed with $(RuCl_2(benzene))_2$, with almost full conversion after 5 h at 40 °C. An even more significant change in reactivity was observed when the transition metal was changed to rhodium, with almost full conversion after only 2.5 h at 40 °C, and iridium with complete conversion in less than 1 h. Even when the precursor loading was decreased to only 0.1 mol%, full conversion could be achieved within 5 h at 40 °C. With the optimal catalyst/ligand (*R*)-**11** and reaction conditions for the CRSC established, we evaluated the scope for a variety of α-disubstituted aldehydes (Table 3). For the synthesis of (*R*)-pantolactone **1a**, the optimized conditions led to a stereoselective aldol addition, transfer hydrogenation, lactonization sequence with an overall yield of 62% and 86:14 enantiomeric enrichment. Other alkyl chains for products **1b** and **1c** gave enantioselectivities of 81:19 e.r. and 70:30 e.r., respectively. Notably, a change to cycloalkyl substituents significantly increased product selectivity to enantiomeric ratios of up to 93:7 for the cyclobutyl product **1d**. Corresponding five- and six-membered derivatives **1e** (e.r. 92:8) and **1f** were also effectively prepared from commercially available starting materials by the catalyst repurposing sequential catalysis. However, a further increase in ring size (**1g**) or the introduction of an aromatic substituent (**1h**) impacted the yield or the selectivity. Over the course of our studies, a kinetic resolution during the transfer hydrogenation for a further enrichment of the enantiopurity was not observed and aldehyde substrates with different α-substituents, for which low diastereoselectivities were observed, represent a current limitation of the method (see SI for details).

Table 3. Substrate Scope of the Catalyst Repurposing Sequential Catalysis for α-Hydroxy-γ-butyrolactones[a]

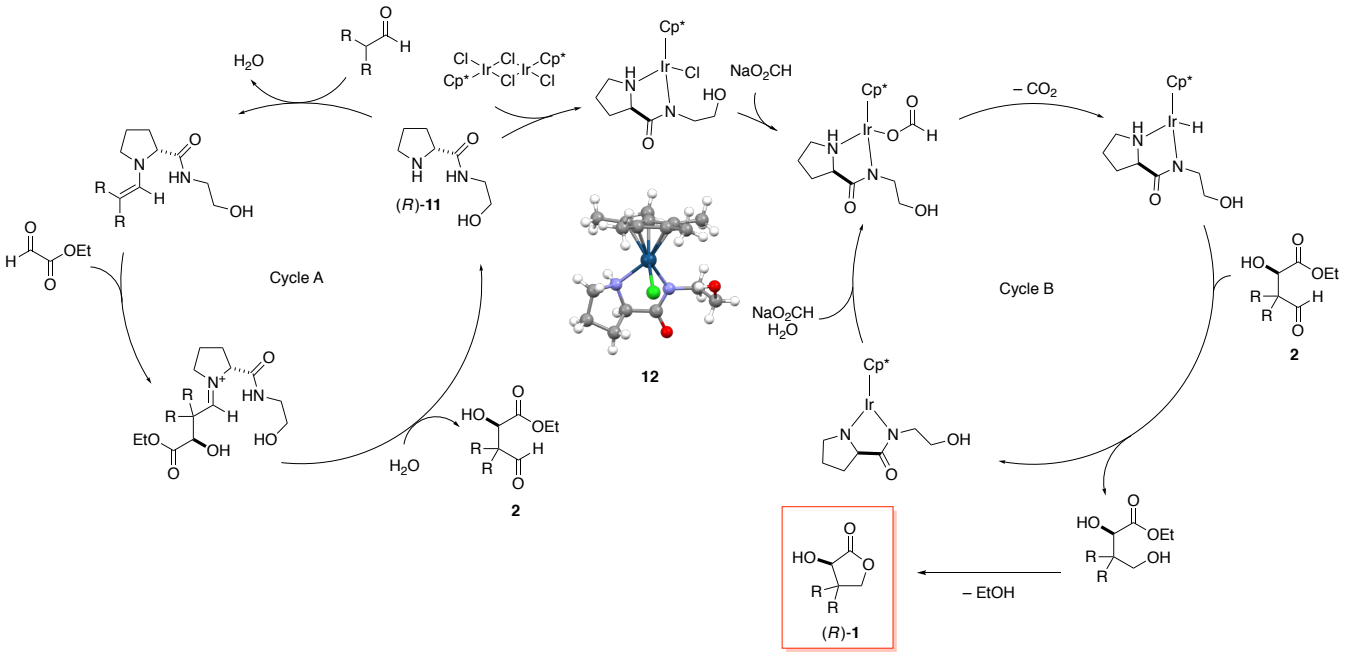


entry	product	yield [%][d]	e.r.	entry	product	yield [%][d]	e.r.
1	 **1a**	62 [84]	86:14	**5**	 **1e**	73 [85]	92:8
2	 **1b**	45 [92]	81:19	**6**	 **1f**	72 [95]	88:12
3	 **1c**	67 [29][e]	70:30	**7**[b]	 **1g**	18 [22]	72:28
4	 **1d**	71 [92]	93:7	**8**[c]	 **1h**	64 [85]	62:38

[a] Reaction conditions: isobutanal (1.00 mmol), ethyl glyoxalate (1.00 mmol, 47 wt.% in toluene), **11** (5.0 - 10 mol%), *t*-BuOH (1.0 mL), 25 °C, 18 - 72 h, $(IrCl_2(Cp^*))_2$ (0.1 mol%), sodium formate (2.00 mmol), water (1 mL), 40 °C, 15 h, isolated yield. [b] 500 µmol scale. [c] 100 µmol scale. [d] Yield in brackets corresponds to isolated aldehyde intermediate. [e] 5.0 mol% **11** were used. [f] 10 mol% **11** were used.

The proposed mechanism of the sequential catalytic transformation involves a first enamine formation from catalyst (*R*)-**11** and isobutanal (Scheme 2) as confirmed by NMR when equimolar amounts of the catalyst in *t*-BuOD-d10 were added under similar conditions to the α-disubstituted aldehyde substrate (see SI for details). Monitoring the enantioselectivity over the course of the subsequent aldol addition reaction revealed only marginal variation, indicating the absence of a competitive uncatalyzed background reaction. Furthermore, a non-linear effect was not noticeable when catalyst **11** with different enantiomeric purities was employed. The catalytic cycle A is then closed by hydrolysis, the secondary amine catalyst is regenerated and the aldol addition intermediate in place for the transfer hydrogenation cycle B. The addition $(IrCl_2Cp^*)_2$ allows to repurpose the regenerated prolinamide (*R*)-**11** as a ligand and upon addition of sodium formate, reduces intermediate **2** to induce a direct lactonization giving the enantioenriched α-hydroxy-γ-butyrolactones. Having observed the remarkable activity of this transfer hydrogenation system, the Ir-complex **12** was prepared by a stoichiometric addition of ligand (*R*)-**11** and Et_3N to $(IrCl_2Cp^*)_2$, which allowed to confirm its structure by X-Ray crystallography (see SI for details).[18] Further studies regarding the influence of the hydroxy arrangement are currently ongoing.

Scheme 2. Mechanistic Proposal



In conclusion, a catalyst repurposing sequential catalysis (CRSC) strategy was developed and employed in the preparation of enantioenriched α-hydroxy-γ-butyrolactones by an economic and operationally simple protocol. The prolinamide organocatalyst was thereby first used in a stereoselective cross aldol addition and subsequently repurposed as ligand for a transition-metal catalyzed transfer hydrogenation. The later addition of the transition-metal precursor upon aldol addition thus allowed to utilize otherwise incompatible aldehyde substrates, which underscores in this scenario the assets of sequential catalysis in comparison with relay, tandem or cascade catalysis. Key industrial intermediates such as the vitamin B_5 precursor (*R*)-pantolactone were readily available in enantioenriched form directly from commercially available starting materials. Considering the multitude of conceivable sequential reactions using amine, NHC and phosphine organocatalysts poised to be repurposed as ligands upon their regeneration, CRSC represents a fascinating possibility for the design of efficient catalytic reaction sequences.

Supporting Information

Experimental procedures and analytical data for the synthesized compounds, including ^1H and ^{13}C NMR spectra and HPLC data. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest. Patent applications were filed by DSM.

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