DOI: 10.1002/adsc.200700216

Domino Hydroformylation/Enantioselective Cross-Aldol Addition

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Received: April 30, 2007; Revised: June 13, 2007

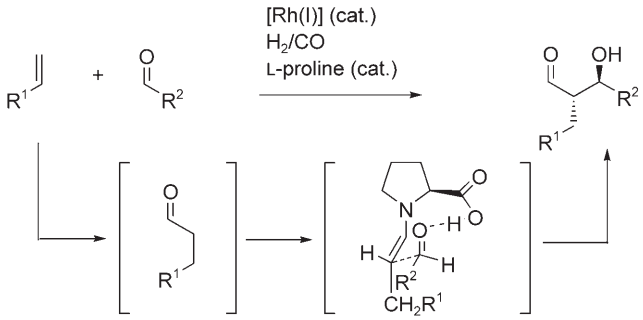
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A domino hydroformylation/enantioselective cross-aldol reaction sequence is reported. Starting from simple alkenes enantiomerically pure aldol addition products, which represent valuable building blocks for polypropionate construction, can be obtained in a one-pot operation.

Keywords: aldol reaction; asymmetric synthesis; domino reactions; homogeneous catalysis; hydroformylation; organocatalysis

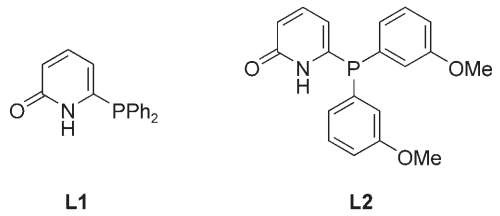
Skeleton expanding operations meeting the conditions of atom economy belong to the most valuable transformations in organic synthesis, provided all levels of selectivity can be controlled.[1] In this context the direct cross-aldol reaction between two enolizable carbonyl components is a highly attractive albeit difficult transformation. Recently, elegant solutions have been developed in order to control chemo- and stereoselectivity[2–4] among which organocatalysis[5,6] has proven particularly useful. Remarkably, even direct and enantioselective cross-aldol coupling between two non-equivalent aldehydes could be realized based on enamine catalysis which has been employed for propionate building block synthesis as well as for the *de novo* construction of carbohydrate derivatives.[7–9] A difficult task in these reactions is to avoid the formation of the homodimer aldols. On the one hand this requires aldehyde components which show significant rate differences in enamine formation. On the other hand, the homo-aldol of the aldehyde component, which is supposed to serve as the nucleophilic donor, has to be suppressed. The current solution to this problem is to keep the concentration of the donor aldehyde low by employing slow syringe pump addition.[7]

As an attractive alternative one might speculate to generate the aldehyde in a low stationary concentration in the course of a catalytic carbon-carbon bond forming reaction meeting the criteria of atom economy such as the hydroformylation of alkenes.[10] This would result in a synthetically appealing domino hydroformylation/organocatalytic aldol addition which starting from alkene feedstocks would furnish enantioenriched aldolates in a one-pot operation (Scheme 1).[11,12]



Scheme 1. Design of a domino hydroformylation/organocatalytic cross-aldol reaction.

A crucial factor for success of this approach is the correct adjustment of the hydroformylation rate to the rate of proline-catalyzed aldol addition since accumulation of the donor aldehyde would facilitate undesired homodimerization of that component. This requires selective hydroformylation catalysts which can operate at temperatures as low as 0–5 °C, which is the temperature range in order to achieve optimal diastereo- and enantioselectivity in the course of the organocatalytic aldol step. Thus, rhodium(I) catalysts modified with either triphenylphosphine or the self-assembling pyridone ligands **L1** and **L2** (Scheme 2) which have proved to furnish particularly reactive and regioselective hydroformylation catalysts at low tem-



L1 L2

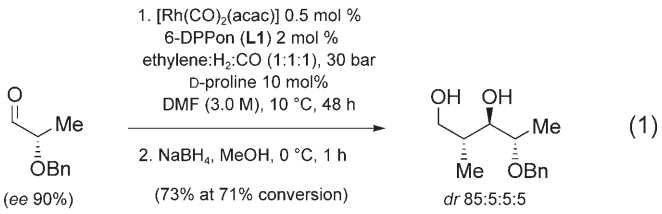
Scheme 2. Structure of the self-assembling ligands **L1** (6-DDPon) and **L2**.

peratures were chosen.[13] In orientating experiments ethylene was selected as the model alkene, since firstly, a domino hydroformylation cross-aldol addition would furnish interesting building blocks for polypropionate construction and secondly, regioselectivity problems in the course of the hydroformylation would be eliminated.

When cylohexanecarbaldehyde was subjected to hydroformylation conditions in the presence of ethylene and L-proline in DMF a smooth domino hydroformylation organocatalytic aldol reaction took place (Table 1). The crude and sensitive aldehyde product was reduced with sodium borohydride to the corresponding 1,3-diol prior to isolation. When employing the most reactive catalyst Rh/**L1** (Table 1, entry 1) a ratio of the desired cross-aldol and the undesired homo-aldol addition product (from *in situ* formed propionaldehyde) of 3:1 was observed. This indicated that the rate of hydroformylation was too fast relative to the organocatalytic aldol process. Employing the less reactive hydroformylation catalyst Rh/**L2** (Table 1, entry 2) led to an improved cross-aldol/homo-aldol ratio. However, optimal results were obtained when the least reactive catalyst Rh/PPh_3 was employed (Table 1, entries 3 and 4). In this case chemoselectivity in favor of the cross-aldol product could be raised to 15:1. Diastereoselectivity and enantioselectivity (99% *ee*) were checked at the diol stage (after transformation to the corresponding acetonide) and are comparable to the results obtained under the syringe pump conditions developed by MacMillan.[7a,14]

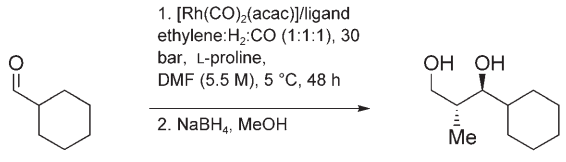
Next, structural variation in the acceptor aldehyde component was studied. Table 2 depicts the optimized reaction conditions for each acceptor aldehyde. In all cases the ratio of cross-aldol to homo-aldol is greater than 10:1. Interestingly, in case of the more electrophilic aryl aldehydes (Table 2, entries 3–8) the more reactive hydroformylation catalyst based on **L1** gave optimal results. This is presumably due to a higher rate for the aldol process, which does not allow accumulation of the donor aldehyde. When salicylaldehyde was used as the acceptor aldehyde the corresponding lactols were isolated (Table 2, entries 6–8). In this case, with L-proline (**1**) or the (*R*)-tetrazole **2**[15] only mediocre enantioselectivities were found (entries 6 and 7). However, employing (*S*)-amine **3**[16] (Scheme 3) as the organocatalyst gave significantly improved enantioselectivity (91% *ee*).

For valuable acceptor aldehydes the reaction conditions can be optimized in order to achieve a maximum conversion of the acceptor component. Thus, domino hydroformylation cross-aldol addition with a lactaldehyde derivative furnished a corresponding stereotriad building block in good yield and stereoselectivity [Eq. (1)].



(*ee* 90%) (73% at 71% conversion) *dr* 85:5:5:5 (1)

Table 1. Optimization of reaction conditions.



99% *ee*

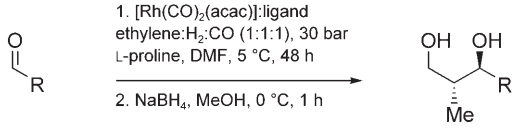
Entry	Conditions[a]	Ligand	CA:HA[b]	Yield[c] [%]	*dr*[b]
1	1:20:20:450	**L1**	3:1	77	95:5
2	1:4:20:450	**L2**	5:1	74	95:5
3	1:20:25:450	PPh_3	15:1	77	94:6
4	1:20:20:400	PPh_3	11:1	81	93:7

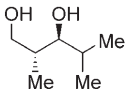
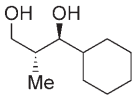
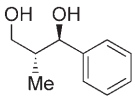
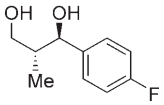
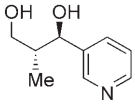
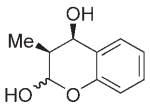
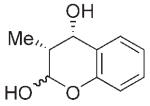
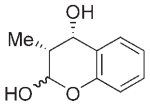
[a] [Rh]:ligand:proline:substrate.
[b] Determined by GC after conversion to the corresponding acetonide.
[c] Isolated yield of purified cross aldol product.[14]

In further experiments extension to terminal alkene systems was explored. Here regioselectivity of the hydroformylation reaction has to be controlled. For this purpose rhodium/6-DPPon (**L1**) was employed as the hydroformylation catalyst which has been developed for highly linear regioselective hydroformylation of terminal alkenes under mild reaction conditions.[13] Thus, both 1-octene (Table 3 entry 1) and vinylcyclohexane (Table 3, entry 2) could be employed to give the cross-aldol products in good diastereo- and excellent enantioselectivity.

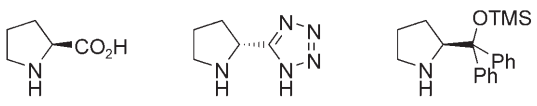
In summary, we have documented the first domino hydroformylation/enantioselective organocatalytic cross-aldol reaction sequence. Starting from simple alkenes enantiomerically pure aldol addition products which represent valuable building blocks for polypropionate construction can be obtained in a one pot operation. Thus, *in situ* hydroformylation as a C–C bond

Table 2. Optimized reaction conditions for each acceptor aldehyde.



Entry	Product	[Rh] (mol%)	Ligand (mol%)	Cat. (mol%)	Yield[a] [%]	*dr*[b]	*ee*[c,d] [%]
1[k]		0.2	PPh_3 (4.4)	**1** (6.0)	76	19:1	98
2[k]		0.25	PPh_3 (5.0)	**1** (5.0)	81	13:1	99
3[l]		0.25	**L1** (1.0)	**1** (5.0)	91	3:1[g]	94
4[l]		0.25	**L1** (1.0)	**1** (6.2)	91[f]	3:1[g]	94
5[l]		0.5	**L1** (1.8)	**1** (4.4)	66[f]	5:1[g]	94
6[i,m]		0.33	**L1** (1.3)	**1** (5.0)	91	5:1	44[e]
7[i,m]		0.33	**L1** (1.3)	**2** (5.0)	99[f]	4:1	67[e]
8[i,j,m]		0.33	**L1** (1.3)	**3** (6.7)	91[f,h]	2:1	91[e]

[a] Isolated yield of purified cross-aldol products (two steps, calculated from conversion of acceptor aldehyde).[14]
[b] *Anti:syn* ratio.
[c] Absolute configuration was assigned by analogy.
[d] Determined by chiral GC unless otherwise indicated; entry 1: Hydrodex β-TBDAC, entries 2–5: Chiraldex (G-TA).
[e] Determined by chiral HPLC (Chiralpak AD-H).
[f] NMR yield.
[g] Determined by NMR.
[h] Homodimer detected in a ratio of 1:5.
[i] The *anti:syn* ratio was determined by NMR after reduction to the corresponding 2-methyl-3-(2-hydroxyphenyl)-1,3-diol. The enantiomeric excess was determined by chiral HPLC after subsequent conversion to the corresponding acetonide.
[j] Run at 15 °C.
[k] [acceptor] = 5.6 M.
[l] [acceptor] = 4.5 M.
[m] [acceptor] = 3.1 M.

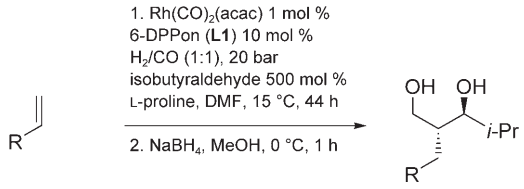


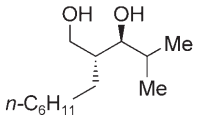
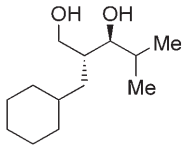
1 2 3

Scheme 3. Structures of organocatalysts employed.

forming reaction as a means to generate the donor aldehyde in the course of a direct cross-aldol reaction is a new and synthetically attractive way to keep the donor aldehyde concentration low, and thus allows the suppression of homo-aldolate formation. The reaction is compatible with a wide range of acceptor aldehydes and can be applied to terminal alkenes em-

Table 3. Domino hydroformylation/cross-aldol addition with terminal alkenes.



Entry	Product	Yield [%][a]	*dr*[b]	*ee* [%][c]
1		86	19:1	97
2		50	10:1	99

[a] Isolated yields of purified cross aldol products (two steps).
[b] Determined by GC after conversion to the corresponding acetonide.
[c] Determined by chiral GC (Chiraldex (G-TA)).

ploying regioselective hydroformylation with self-assembling catalyst Rh/6-DPPon (**L1**).

Experimental Section

General Procedure for the Domino Reaction

[$Rh(CO)_2acac$] (7.8 mg, 0.030 mmol), triphenylphosphine (158.6 mg, 0.604 mmol), L-proline (69.6 mg, 0.604 mmol) and cyclohexanecarbaldehyde (1.36 g, 12.4 mmol) were dissolved in DMF (2.2 mL). The solution was transferred to an autoclave, pressurized (30 bar, ethylene:H_2:CO 1:1:1), and the reaction mixture stirred for 48 h at 5 °C. The reaction mixture was then diluted with methanol (16 mL), cooled down to 0 °C, and $NaBH_4$ (0.90 g, 24.0 mmol) was added portionswise. After the reduction was complete, the reaction mixture was further diluted with ethyl acetate (50 mL) and hydrolyzed with water (20 mL) and saturated aqueous NH_4Cl solution (20 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3×75 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. Flash chromatography of the residue [alumina (deactivated), cylohexane:ethyl acetate (from 4:1 to 1:1)] furnished (2*R*,3*S*)-3-cyclohexyl-2-methyl-1,3-propane diol as a colourless oil; yield: 408 mg (81 % based on conversion), 99 % *ee* determined by chiral GC (for details see Table 1).

Supporting Information

Spectroscopic and analytical data for all new compounds as well as experimental procedures are available as Supporting Information.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (International Research Training School "Catalysts and Catalytic Reactions for Organic Synthesis" GRK 1038) the Alfried Krupp Award for young university teachers of the Krupp foundation (to BB).

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[14] It is important to note that under cross-aldol reaction conditions reported in ref.[7a] an excess 2–10 equivs. of the acceptor aldehyde is required. Hence, the isolated yields of pure cross-aldol products in this work are (within experimental errors) the same as those reported under syringe pump addition in ref.[7a]

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