Asymmetric Aldol Reaction Using Immobilized Proline on Mesoporous Support

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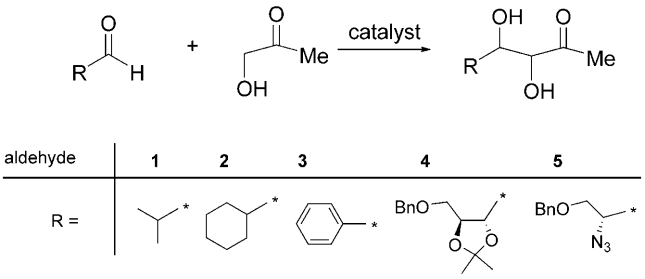
Abstract: The aldol reaction of hydroxyacetone with different aldehydes using immobilized proline on a mesoporous support, assisted by heat and microwaves, has been explored. It was found that heterogenized L-proline on MCM-41 catalyzed aldol reactions in both hydrophilic and hydrophobic solvents, and provided stereoselectivities in some cases complementary to the homogeneous catalyst. The heterogeneous catalysts could be reused without significant lost of stereoselectivity.

Keywords: aldol reaction; arylmethoxyacetic acids; mesoporous material; organic catalysis; L-proline; supported catalysts

Introduction

The aldol reaction is recognized as being one of the most powerful and popular methods for the construction of C–C bonds. Organocatalysis,[1] in particular the use of the amino acid proline[2] and its derivatives,[3] has recently experienced a renaissance in catalytic asymmetric aldol condensations. The main advantages of this method are that the reaction can be performed in a stereoselective manner, under mild conditions and without the need of any metal. In addition, both enantiomers of proline are available. From a practical point of view, it would be desirable to have the catalyst immobilized so that the product purification can be facilitated and the catalyst recycled. One method to immobilize the catalyst is to covalently anchor the proline onto a solid carrier. Functionalized pure silica mesoporous materials have been shown to be excellent materials for the preparation of heterogenized catalysts.[4]

Here we describe our results of a comparative study of aldol reactions of different aldehydes with hydroxyacetone using proline either free or covalently anchored to mesoporous MCM-41 (Scheme 1). We were interested in this reaction since it furnishes 1,2-diols which may be used in the synthesis of carbohydrate analogues as inhibitors of glycosidases and glycosyltransferases.[5]



Scheme 1. Aldol condensation between hydroxyacetone and different aldehydes catalyzed by L-proline or mesoporous material.

Results and Discussion

Synthesis of the Catalyst

The synthesis of the heterogenized catalyst was carried out following the route described in Scheme 2.

Several mesoporous and lamellar siliceous materials with different topologies were used to heterogenize proline derivatives **11a** and **11b**. The results (summarized in Table 1) indicated that functionalized MCM-41 with L-proline (MCM41-Pro) gave the best results. Interestingly, the heterogenized catalyst could be reused for a second and third run without significant lost of stereoselectivity, but with a slight reduction of the yield, probably due to a loss of catalytic material.

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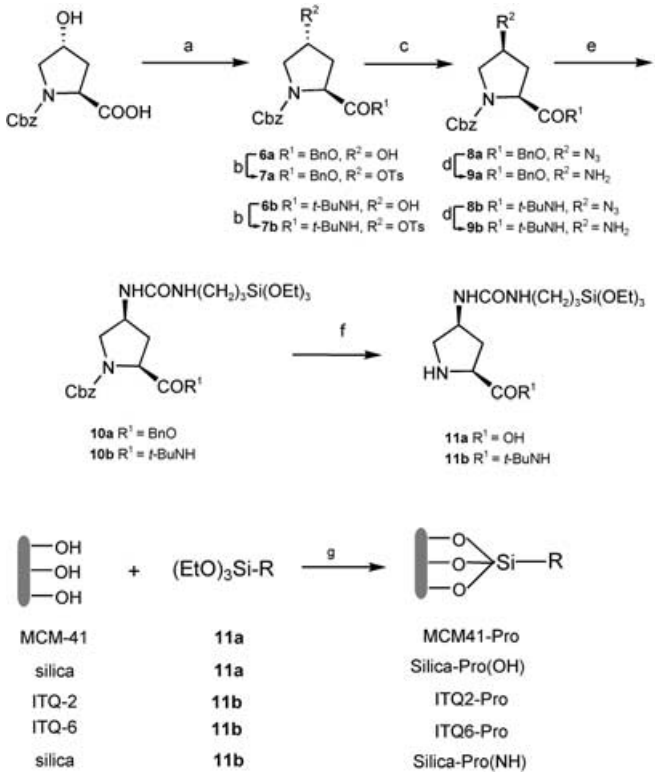


Scheme 2. Reagents and conditions: a) (i) Et_3N, ClCOOEt, THF, 0 °C, 30 min; (ii) BnOH, reflux, 24 h, 70% for **6a**; *t*-$BuNH_2$, reflux, 2 h, 89.5% for **6b**; b) TsCl, Py, r.t., 48 h, 80% for **7a**; 100% for **7b**; c) NaN_3, DMF:water, 70 °C, 48 h, 80% for **8a**;100% for **8b**; d) Pd/C (5%), AcOEt, 20 h, 89% for **9a**; 97% for **9b**; e) $(EtO)_3Si(CH_2)_3NCO$, CH_2Cl_2, r.t., 18 h, 100%; f) Pd/C, cyclohexene, EtOH, r.t., 15 min for **11a**;1 h for **11b**, 100%; g) toluene, reflux, 18 h.

Table 1. Asymmetric aldol reactions between **1** and **3** with hydroxyacetone catalyzed by different heterogenized catalysts.

Aldehyde	Catalyst[c]	Yield [%]	d.r.[d]
1[a]	MCM41-Pro (0.47)	45	>20:1
1[a, e]	MCM41-Pro (0.47)	42	>20:1
1[a, f]	MCM41-Pro (0.47)	40	>20:1
1[a]	ITQ2-Pro (0.64)	40	>20:1
1[a]	ITQ6-Pro (0.33)	13	>20:1
1[a]	Silica-Pro(OH) (0.52)	30	>20:1
1[a]	Silica-Pro(NH) (0.43)	20	>20:1
3[b]	MCM41-Pro (0.47)	55	1:1.4
3[b, e]	MCM41-Pro (0.47)	55	1:1.4
3[b, f]	MCM41-Pro (0.47)	50	1:1.3
3[b]	ITQ2-Pro (0.64)	40	1:1.3
3[b]	ITQ6-Pro (0.33)	20	1:1
3[b]	Silica-Pro(OH) (0.52)	27	1:1
3[b]	Silica-Pro(NH) (0.43)	20	1:1.3

[a] Room temperature, 24 h, DMSO.
[b] 90 °C, 24 h, DMSO.
[c] The catalyst loading (mmol/g) is shown in parenthesis.
[d] d.r. = *anti*/*syn*. The ratio was determined by GC.
[e] The catalyst was reused for a second run.
[f] The catalyst was reused for a third run.

Aldol Condensations

Once we had found MCM41-Pro to be the best heterogenized catalyst, we next studied condensations with different aldehydes using this catalyst and, for comparative purpose, L-proline (table 2). While the proline-catalyzed reactions require highly polar solvents (DMSO, DMF, mixture of DMSO/water), heterogenized catalyst MCM41-Pro allowed us to use non-polar solvents. The reactions with L-proline were performed following the described conditions for aldehydes **1**–**3**[2c] at room temperature for 24–72 h. In the presence of MCM41-Pro, mixtures were heated in DMSO or toluene at 90 °C for 24–72 h. The absolute configurations of the 1,2-diol products have been assigned from the ^{1}H NMR spectra of their (*R*)- and (*S*)-arylmethoxyacetic acid diesters, as discussed below. L-Proline-catalyzed reactions with aldehydes **1**–**3** gave similar results as reported previously.[2c] In general, yields were higher using the homogeneous conditions, although rather dependent on the type of aldehyde. Concerning the stereoselectivity, for aldehydes **1** and **2** both proline and MCM41-Pro gave the highest diastereo- and enantioselectivities, the *anti*-(1*S*,2*S*)-diol being the main product. However, aldehydes **3**–**5** afforded different stereoselectivities depending on the catalyst. Benzaldehyde **3** in the presence of proline gave the *anti*-1,2-diol in a 2.5:1 diastereoselectivity ratio (entry 7), however with MCM41-Pro a mixture was obtained in which the *syn*-(1*S*,2*R*)-diol slightly predominated (entries 8 and 9). In the case of the L-threose derivative **4**, the diastereoselectivity of the reaction reversed upon changing from L-proline (d.r., 2.8:1) to MCM41-Pro/toluene (d.r., 1:2.8). For the azido aldehyde **5**, the L-proline-catalyzed reaction gave the *anti*-diol with good yield and stereoselectivity, while the heterogenized catalyst afforded poor results. Therefore, these results indicate that the immobilization of proline on a mesoporous silica support gives a heterogenized catalyst for aldol reactions that works in hydrophobic solvents and provides stereoselectivities in some cases complementary to those of the homogeneous catalyst.

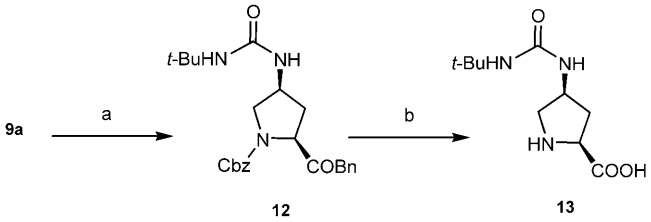
In order to know if the stereoselectivity changes observed with MCM41-Pro could be ascribed to the presence of the substituent at C-4 of the proline ring, we prepared a model compound having a referable *t*-butoxycarbamate group at this position (**13**, Scheme 3). Condensations of aldehydes **1**–**4** with hydroxyacetone in the presence of **13** under the conditions applied to MCM41-Pro gave stereoselectivities similar to those obtained with L-proline (Table 3).

Therefore, the stereoselectivity changes obtained with MCM41-Pro as compared to L-proline must be related to interactions of the reactants with the solid support. One possibility for the case of aldehydes **4** and **5**, which gave the most important changes of stereoselectivity, could be the development of hydrogen bonding-type interactions between the silanols on the support and some

Table 2. Asymmetric aldol reactions catalyzed by L-proline and MCM41-Pro.

Entry	Aldehyde	Catalyst[a]	Solvent	Yield [%][b]	d.r.[c]	ee [%][d]
1	**1**	A	DMSO	75	>20:1	>99
2	**1**	B	DMSO	55	>20:1	>99
3	**1**	B	Toluene	55	>20:1	>99
4	**2**	A	DMSO	55	>20:1	80
5	**2**	B	DMSO	60	>20:1	70
6	**2**	B	Toluene	55	>20:1	70
7	**3**	A	DMSO	80	2.5:1	80
8	**3**	B	DMSO	55	1:1.4	70
9	**3**	B	Toluene	60	1:1.6	70
10	**4**	A	DMSO	70	2.8:1	–
11	**4**	B	DMSO	72	1:1.6	–
12	**4**	B	Toluene	60	1:2.8	–
13	**5**	A	DMSO	75	6:1	–
14	**5**	B	DMSO	30	1:1.4	–
15	**5**	B	Toluene	15	1:1.6	–

[a] A = L-proline; B = MCM41-Pro (0.52 mmol/g).
[b] Yield calculated on isolated product.
[c] d.r. = *anti/syn*. The ratio was determined by ^{1}H NMR or GC.
[d] The ee values were determined by chiral-phase GC or by ^{1}H NMR after double derivatization (see text). All values are referred to the major diastereomer.



Scheme 3. Reagents and conditions: a) *t*-BuNCO, CH_2Cl_2, r.t., 1 h, 100%; b) Pd/C, cyclohexene, EtOH, reflux, 15 min, 100%.

Table 3. Asymmetric aldol reaction catalyzed by **13** in DMSO.

Aldehyde	*t* [h]	Yield [%]	d.r.[a]	ee [%][b]
1	48	30	>20:1	>99
2	72	20	>20:1	>99
3	24	20	2.2:1	80
4	24	20	2.8:1	–

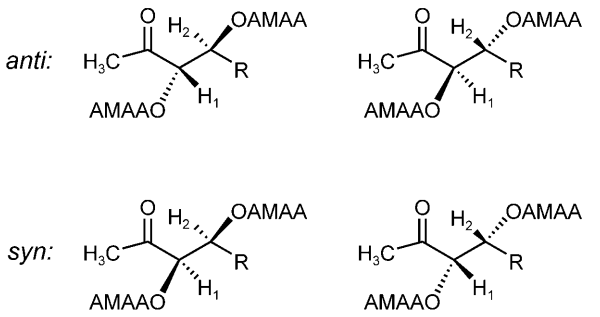
[a] d.r. = *anti/syn*. The ratio was determined by GC.
[b] The ee values were determined by chiral-phase GC. All values are referred to the major diastereomer.

oxygen or nitrogen atom of the R substituent in the aldehyde, forcing an orientation of the reactant which leads to the *syn*-diol product. This interaction would be favored in non-polar toluene, which would explain the increase of *syn*-diol formation in the reaction of **4** catalyzed by MCM41-Pro when changing from DMSO to toluene (see entries 11 and 12 in Table 1). In addition, the silanol groups of the support surface could interact with the carbonyl group of the aldehyde resulting in polarization of the group and, eventually, increasing the reaction rate.[6] This effect would account for the higher yields of condensation products obtained with MCM41-Pro as compared to the model **13**. In spite of the advantages that the heterogenized catalyst could offer, the harsh conditions required for condensations (90 °C and long reaction times) may lead to decomposition of aldehyde and/or products. Indeed, this is probably the cause of the lower yield obtained in some cases

Table 4. Asymmetric aldol reactions catalyzed by L-proline and MCM41-Pro in DMSO with the assistance of microwave heating.

Aldehyde	Catalyst[a]	*t* [min]	Yield [%]	d.r.[b]	ee [%][c]
1	A	10	60	>20:1	>99
1	B	10	60	>20:1	>99
2	A	10	90	>20:1	>99
2	B	10	90	>20:1	>99
3	A	10	65	2.2:1	75
3	B	30	70	1:1.4	80
4	A	10	60	2.1:1	–
4	B	25	60	1:1.6	–
5	A	10	65	3:1	–
5	B	15	55	1:1.3	–

[a] A = L-proline; B = MCM41-Pro (0.52 mmol/g).
[b] d.r. = *anti/syn*. The ratio was determined by ^{1}H NMR or GC.
[c] The ee values were determined by chiral phase GC. All values are referred to the major diastereomer.



$\Delta\delta^{RS}$	H-1	H-2	CH_3	R
anti (S,S)	>0	<0	>0	<0
anti (R,R)	<0	>0	<0	>0
syn (R,S)	>0	>0	-	-
syn (S,R)	<0	<0	-	-

Figure 1. Diagnostic $\Delta\delta^{RS}$ signs for the four possible stereoisomers.

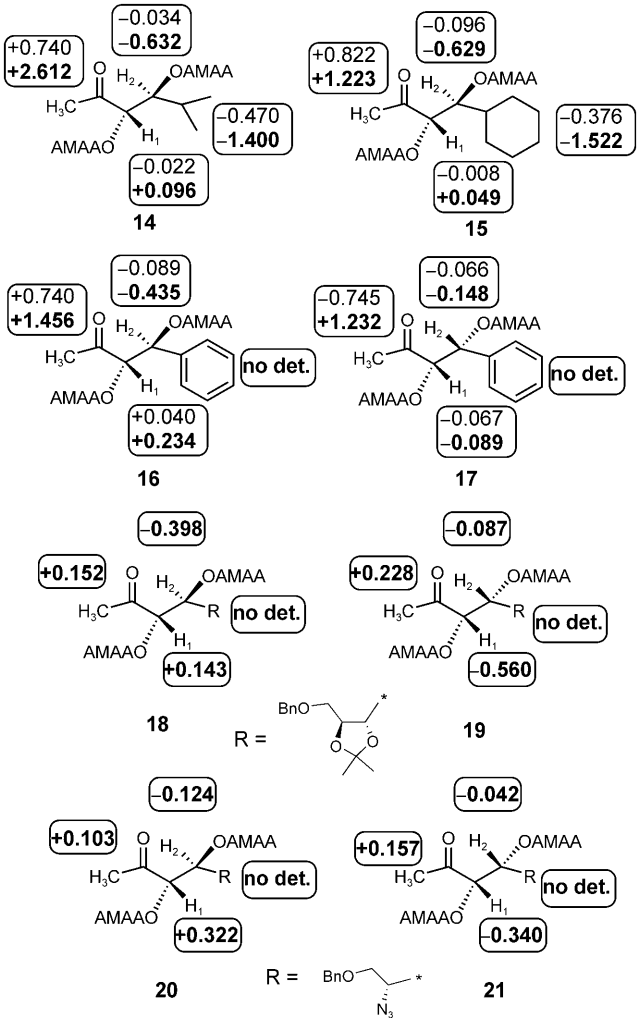


Figure 2. $\Delta\delta^{RS}$ values for diester derivatives of aldol products. Plain and bold numbers correspond to values from MPA and 9-AMA, respectively.

with MCM41-Pro compared with proline. In an attempt to overcome this problem, the reactions were tried under less aggressive conditions by assistance of microwaves. Thus, aldehydes **1**–**5** were reacted with hydroxyacetone in the presence of MCM41-Pro under microwave irradiation using a household microwave oven (900 W). For comparative purposes proline-catalyzed reactions were also tested under these conditions. The results are summarized in Table 4. Reaction times were drastically reduced, providing aldols at room temperature in only few minutes. Moreover, under these conditions yields for MCM41-Pro were improved with most of the aldehydes, being most noticeable in the cases of **2** (from 55 to 90%) and **5** (from 30 to 55%).

Determination of Absolute Configuration

To assign the absolute configuration of the 1,2-diol products we employed a recently described method involving the formation of the corresponding diesters with (*R*)- and (*S*)-arylmethoxyacetic acids (AMAA) and comparison of the $\Delta\delta^{RS}$ signs of their ^{1}H NMR spectra.[7] Following this procedure, the diagnostic $\Delta\delta^{RS}$ signs for the four possible stereoisomers of our aldol products are represented in Figure 1. Since the absolute configuration of the main reaction product of aldehydes **1**–**3** using L-proline was reported,[2c] it was used as a probe for testing the reliability of this assignment method. In Figure 2 the signs of the $\Delta\delta^{RS}$ experimentally obtained for protons considered of diagnostic value of the aldol products, after derivatization with (*R*)- and (*S*)-methoxyphenylacetic acid (MPA) and 9-anthrylmethoxyacetic acid (9-AMA), are shown.

In the case of the diesters **14** and **15**, the absolute configurations determined using the 9-AMA were in agreement with that reported for the corresponding diol. However, the use of MPA gave smaller $\Delta\delta^{RS}$ values for the protons bound to the new chiral centers (H-1 and H-2) and the signs for H-1 in diesters **14** and **15** did not match with the expected configuration. To understand these differences in sign, the structures of MPA diesters **14** and **15** were minimized (HTF, 6-31G*, see Supporting Information) and it was found that the more stable conformation did not correspond with that established by Riguera et al. to have an effective shielding/deshielding effect. Due to the higher accuracy using 9-AMA, the absolute configurations of the aldol products from aldehydes **4** and **5** were determined by analysis of their 9-AMA diesters **18**–**21**. In this way the *anti*-diol products were characterized as the (1*S*,2*S*)-configured diol (die-

ster derivatives **18** and **20**), and the *syn*-product as (1*S*,2*R*)-diol (diester derivatives **19** and **21**).

Conclusion

In conclusion, a heterogeneous methodology for direct asymmetric aldol condensations where the catalyst can be retrieved and recycled has been developed by heterogenizing proline on the mesoporous material MCM-41. Condensations of some aldehydes with hydroxyacetone have resulted in aldol products with moderate to good yields and stereoselectivities, in some cases leading to the formation of the *syn*-diol as main product. With the assistance of microwave heating, reaction times were drastically decreased and yields were generally improved. In addition, we have shown that derivatization of aldol products using 9-AMA, as described previously,[7] is an appropriate method to assign by NMR the absolute configuration of aldols.

Experimental Section

(2*S*,4*R*)-1,2-Dibenzyloxycarbonyl-4-hydroxypyrrolidine (6a)

Ethyl chloroformate (1.43 mL, 15 mmol) was added dropwise to a stirred solution of (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxyproline (4 g, 15 mmol) and triethylamine (2.1 mL, 15 mmol) in anhydrous THF (22 mL) at 0 °C. After stirring at this temperature for 30 min, benzyl alcohol (2.5 mL, 20 mmol) was added and the reaction mixture was refluxed for 24 hours. The resulting solid was removed by filtration and washed with AcOEt. The filtrate was concentrated under vacuum and the residue dissolved in AcOEt (20 mL) and washed with water (3 × 40 mL), $NaHCO_3$ (3 × 40 mL) and NaCl (3 × 40 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexane/AcOEt, 2:1) to afford **6a** as a pale yellow oil; yield: 3.9 g (70%); $[\alpha]_D^{25}$: $+60^0$ (*c* 2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 10H, Ph), 5.32–4.98 (m, 4H, $2CH_2Ph$), 4.60–4.48 (m, 2H, H-2, H-4), 3.72–3.45 (m, 2H, CH_2-5), 2.4–2.0 (m, 2H, CH_2-3); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 173.7, 152.5, 136.2, 135.7, 135.4, 135.0,134.7, 134.4, 128.5, 128.0, 65.6, 60.4, 59.2, 58.9, 52.5, 35.2; MS (EI): *m*/*z* = 356.3 (M + 1; (calcd. for M^+: 355.1), 378.3 (M + 23); anal. calcd. for $C_{20}H_{21}NO_5$: C 67.5, H 5.9, N 3.9%; found: C 67.9, H 6.2, N 4.2%.

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-*tert*-butylaminocarbonyl-4-hydroxypyrrolidine (6b)

Ethyl chloroformate (7.05 g, 65 mmol) was added dropwise to a stirred solution of (2*S*,4*R*)-1-benzyloxycarbonyl-4-hydroxyproline (17.21 g, 65 mmol) and triethylamine (6.56 mL, 65 mmol) in anhydrous THF (80 mL) at 0 °C. After 30 min, *t*-butylamine (6.63 g, 91 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. The resulting solid was removed by filtration and washed with AcOEt. After 1 h at this temperature, the resulting solid was removed by filtration and washed with AcOEt. The filtrate was concentrated under vacuum and the residue was dissolved in AcOEt (20 mL) and washed with water (3 × 40 mL), $NaHCO_3$ (3 × 40 mL) and NaCl (3 × 40 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated. The residue was recystallized from (toluene/cyclohexane) to afford **6b**; yield: 17.2 g (89.5%); mp 97–99 °C; $[\alpha]_D^{25}$: −12.7 (*c* 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5H, Ph), 5.22–5.15 (m, 2H, CH_2Ph), 4.52–4.49 (m, 1H, H-4), 4.32 (m, 1H, H-2), 3.62–3.55 (m, 2H, CH_2-5), 2.39–2.19 (m, 2H, CH_2-3), 1.2 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 169.7, 154.5, 136.2, 128.5, 128.3, 128.1, 65.4, 60.0, 59.2, 51.9, 35.2, 28.4; MS (EI): *m*/*z* = 321.2 (M + 1; calcd. for M^+: 320.1); Anal. calcd. for $C_{17}H_{24}N_2O_4$: C 63.7, H 7.5, N 8.7%; found: C 63.9, H 7.5, N 8.6%.

(2*S*,4*R*)-1,2-Dibenzyloxycarbonyl-4-(*p*-toluenesulfonyloxy)pyrrolidine (7a)

To a cooled solution (0 °C) of **6a** (3.9 g, 10.9 mmol) in dry pyridine (10 mL) was added *p*-toluenesulfonyl chloride (2.58 g, 13.6 mmol). The temperature was allowed to gradually rise to room temperature over 1 h. After 48 h the solvent was evaporated and the crude reaction product was purified by column chromatography (hexane/AcOEt, 4:1) to give **7a** as a yellow oil; yield: 4.46 g (80%); $[\alpha]_D^{25}$: −25.3 (*c* 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.69 (m, 4H, Ph_{Ts}), 7.4–7.2 (m, 10H, Ph), 5.22–5.0 (m, 5H, $2CH_2Ph$, H-4), 4.56–4.48 (m, 1H, H-2), 3.79–3.64 (m, 2H, CH_2-5), 2.65–2.50(m, 1H, $C\underline{H}_B$-CH_A-3), 2.48 (s, 3H, CH_3Ph_{Ts}), 2.3 (m, 1H, CH_B-$C\underline{H}_A$-3); MS (EI): *m*/*z*= 510.3 (M + 1, calcd. for M^+: 509.1), 532.3 (M + 23); anal. calcd. for $C_{27}H_{27}NO_7S$: C 63.6, H 5.3, N 2.7, S 6.2%; found: C 63.2, H 5.6, N 2.6, S 6.8%.

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-*tert*-butylaminocarbonyl-4-(*p*-toluenesulfonyloxy)pyrrolidine (7b)

To a cooled solution (0 °C) of **6b** (4 g, 12 mmol) in dry pyridine (12.1 mL) was added *p*-toluenesulfonyl chloride (2.86 g, 15 mmol). The temperature was allowed to gradually rise to room temperature over 1 h. After 48 h the solvent was evaporated and the crude reaction product was purified by column chromatography (hexane/AcOEt, 6:1) to give **7b** as a yellow oil; yield: 5.9 g (100%); $[\alpha]_D^{25}$: −12.7 (*c* 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.22 (m, 9H, Ph), 5.22–5.0 (m, 3H, CH_2Ph, H-4), 4.32–4.22 (m, 1H, H-2), 3.92–3.55 (m, 2H, CH_2-5), 2.73–2.10 (m, 2H, CH_2-3), 2.48 (s, 3H, CH_3Ph_{Ts}), 1.2 (s, 9H, *t*-Bu); MS (EI): *m*/*z* = 475.2 (M + 1, calcd. for M^+: 474.1); anal. calcd. for $C_{24}H_{30}N_2O_6S$: C 60.7, H 6.3, N 5.9, S 6.7%; found: C 60.7, H 6.4, N 6.2, S 6.3%.

(2*S*,4*S*)-4-Azido-1,2-dibenzyloxycarbonylpyrrolidine (8a)

Sodium azide (1.14 g) was dissolved in a mixture of DMF:water (40:6 mL) and **7a** (4.46 g, 8.8 mmol) was added. The mixture

was heated at 70 °C for 48 h. After this time solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether (20 mL), washed with NaCl saturated (3 × 30 mL) and dried over Na_2SO_4. After evaporation of the solvent the residue was chromatographed (hexane/AcOEt, 1:1) to afford **8a** as a pale oil; yield: 3.34 g (80%); $[\alpha]_D^{25}$: −33.5 (*c* 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.32 (m, 5H, Ph), 5.30–4.98 (m, 4H, $2CH_2Ph$), 4.49–4.32 (m, 1H, H-4), 4.16–3.99 (m, 1H, H-2), 3.74–3.60 (m, 1H, $C\underline{H}_B$-CH_A-5), 3.53–3.39 (m, 1H, CH_B-$C\underline{H}_A$-5), 2.49–2.30 (m, 1H, CH_B-$C\underline{H}_A$-3), 2.18–2.12 (m, 1H, CH_B-$C\underline{H}_A$-3); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 171.0, 154.2, 136.2, 135.4, 135.4, 135.0,135.4, 134.7, 128.5, 128.0, 67.2, 67.1, 59.2, 58.0 , 52.3, 35.5; MS (EI): *m*/*z* = 381.2 (M + 1, calcd. for M^+: 380.2), 403.3 (M + 23); anal. calcd. for $C_{20}H_{20}N_4O_4$: C 63.1, H 5.3, N 15.2%; found: C 63.0, H 5.3, N 15.4%.

(2*S*,4*S*)-4-Azido-1-benzyloxycarbonyl-2-*tert*-butylaminocarbonylpyrrolidine (8b)

To a solution of sodium azide (0.9 g, 14 mmol) in DMF (50 mL) **7b** (5 g, 10 mmol) was added. The mixture was heated at 70 °C for 48 h. After this time solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether (20 mL), washed with NaCl saturated (3 × 30 mL) and dried over Na_2SO_4. After evaporation the crude reaction product was chromatographed (hexane/AcOEt, 1:1) furnishing **8b** as a pale oil; yield: 3.6 g (100%); $[\alpha]_D^{25}$: +11.0 (*c* 1, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.22 (m, 5H, Ph_{Ts}), 5.32–5.0 (m, 2H, CH_2Ph), 4.42–4.33 (m, 1H, H-4), 4.2 (t, 1H, CH_2-3), 3.73–3.42 (m, 2H, CH_2-5), 2.68–2.2 (m, 2H, CH_2-3), 1.3 (s, 9H, *t*-Bu); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 169.7, 155.5, 136.0, 128.5, 128.2, 128.0, 67.6, 60.4, 58.9, 52.5, 34.5, 28.4; MS (EI): *m*/*z* = 346 (M + 1, (calcd. for M^+: 345.1); anal. calcd. for $C_{17}H_{23}N_5O_3$: C 59.1, H 6.7, N 20.2%; found: C 59.5, H 6.7, N 20.6%.

(2*S*,4*S*)-4-Amino-1,2-dibenzyloxycarbonylpyrrolidine (9a)

Azide **8a** (2.46 g, 6.36 mmol) was dissolved in AcOEt (21 mL) and Pd/C (5%) was added (90 mg). The suspension was then stirred under hydrogen for 20 h. After this time, the solution was filtered through Celite® and washed with AcOEt. Removal of the solvent under reduced pressure and purification by column chromatography (CH_2Cl_2/MeOH 20:1) afforded amine **9a** as a yellow oil; yield: 2.32 g (89%); $[\alpha]_D^{25}$: +8.87 (*c* 1, $CHCl_3$). ^{1}H MNR (300 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 10H, Ph), 5.20–4.93 (m, 4H, $2CH_2Ph$), 4.40–4.327 (m, 1H, H-4), 3.73–3.63 (m, 1H, H-2), 3.52–3.25 (m, 1H, $C\underline{H}_B$-CH_A-5), 3.30–3.22 (m, 1H, CH_B-$C\underline{H}_A$-5), 2.44–2.34 (m, 1H, CH_B-$C\underline{H}_A$-3), 1.83–1.74 (m, 1H, CH_B-$C\underline{H}_A$-3); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 173.1, 155.12, 136.6, 135.63, 128.80, 128.66,128.40, 128.26, 128.21, 128.06, 67.34, 67.13, 58.38, 55.84, 50.46, 35.5; MS (EI): *m*/*z* = 355.2 (M + 1, (calcd. for M^+: 354.1), 377.2 (M + 23); anal. calcd. for $C_{20}H_{20}N_2O_4$: C 67.7, H 6.2, N 7.9%; found: C 67.7, H 6.5, N 8.2.

(2*S*,4*S*)-4-Amino-1-benzyloxycarbonyl-2-*tert*-butylaminocarbonylpyrrolidine (9b)

Azide **8b** (500 mg, 1.44 mmol) was dissolved in AcOEt (7 mL) and Pd/C (5%) was added (5 mg). The suspension was then stirred under hydrogen for 16 h. After this time, the solution was filtered through Celite® and washed with AcOEt. Removal of the solvent under reduced pressure and purification by column chromatography (CH_2Cl_2/MeOH, 20:1) afforded amine **9b** as a yellow oil; yield: 450 mg (97%); $[\alpha]_D^{25}$: −13.7 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.22 (m, 5H, Ph), 5.22–5.10 (m, 2H, CH_2Ph), 4.21–4.17 (m, 1H, H-4), 3.73–3.64(m, 2H, H-2), 3.66–3.58 (m, 1H, CH_B-$C\underline{H}_A$-5), 3.32–3.24 (m, 1H, $C\underline{H}_B$-CH_A-5), 2.3–2.22 (m, 1H, CH_2-3), 1.3 (s, 9H, *t*-Bu);^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 171.3, 155.3, 136.3, 128.2, 127.8, 127.7, 67.7, 61.1, 55.7, 50.7, 50.2, 38.2. MS (EI): *m*/*z* = 320.2 (M + 1, (calcd. for M^+: 319.1); anal. calcd. for $C_{17}H_{25}N_3O_3$: C 63.9, H 7.8, N 13.1%; found: C 64.0, H 7.8, N 13.2%

(2*S*,4*S*)-1,2-Dibenzyloxycarbonyl-4-(3-triethoxysilylpropylaminocarbonylamino)pyrrolidine (10a)

To a solution of **9a** (2.20 g, 6.21 mmol) in anhydrous CH_2Cl_2 (32 mL) was added triethoxysilylpropyl isocyanate (1.53 g, 6.21 mmol). The reaction mixture was stirred under Ar at room temperature for 18 h. Evaporation of the solvent gave **10a** which was used without further purification; yield: 3.69 g (100%); $[\alpha]_D^{25}$: −16.5 (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 10H, Ph), 5.23–4.87 (m, 4H, 2 CH_2Ph), 4.47–4.31 (m, 1H, H-4), 4.09–4.02 (m, 1H, H-2), 3.8 (dt, 6H, $CH_3C\underline{H}_2OSi$), 3.6–3.5 (m, 2H, CH_2-5), 3.1 (m, 2H, $C\underline{H}_2NHCONH$), 2.4–1.9 (m, 2H, $C\underline{H}_2$-3), 1.5 (m, 2H, $C\underline{H}_2$ $CH_2NHCONH$), 1.2 (t, 9H, $C\underline{H}_3CH_2OSi$); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 174.0, 157.3, 136.0, 129.2, 128.1, 127.4, 127.1, 67.0, 58.3, 57.9, 54.2, 49.4, 44.7, 37.2, 23.4, 18.3, 8. MS (EI): *m*/*z* = 624.5 (M + 23, calcd. for M^+: 601.2); anal. calcd. for $C_{30}H_{43}N_3O_8Si$: C 59.8, H 7.2, N 6.9%; found: C 59.5, H 7.3, N 7.0%.

(2*S*,4*S*)-1-Benzyloxycarbonyl-2-*tert*-butylaminocarbonyl-4-(3-triethoxysilylpropylaminocarbonylamino)pyrrolidine (10b)

To a solution of **9b** (924 mg, 2.89 mmol) in anhydrous CH_2Cl_2 (15 mL) was added triethoxysilylpropyl isocyanate (716 mg, 2.89 mmol). The reaction mixture was stirred under Ar at room temperature for 18 h. Evaporation of the solvent gave **10b** that was used without further purification; yield: 1.635 g (100%); $[\alpha]_D^{25}$: −12.4 (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.1 (m, 5H, Ph), 5.12–4.87 (m, 2H, CH_2Ph), 4.55–4.31 (m, 1H, H-4), 4.12–3.94 (m, 1H, H-2), 3.99–3.72 (dt, 6H, $CH_3C\underline{H}_2OSi$), 3.84–3.33 (m, 2H, CH_2-5), 3.27–3.15 (m, 2H, $C\underline{H}_2NHCONH$), 2.10–1.92 (m, 2H, $C\underline{H}_2$-3), 1.74–1.55 (m, 2H, $C\underline{H}_2CH_2NHCONH$), 1.3 (s, 9H, *t*-Bu), 1.1 (t, 9H, $C\underline{H}_3CH_2OSi$), 0.66 (t, 2H, CH_2Si); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 172.0, 157.8, 156.6, 137.0, 128.6, 128.3, 128.2, 67.4, 61.2, 58.5, 55.8, 51.1, 50.2, 43.2, 32.5, 28.7, 28.5,

8.1; MS (EI): $m/z = 567.0$ (M+1, calcd. for M^+: 566.3; anal. calcd. for $C_{27}H_{46}N_4O_7Si$ C 57.2, H 8.1, N 9.8%; found: C 57.4, H 8.2, N 9.9%.

(2*S*,4*S*)-2-Carboxy-4-(3-triethoxysilylpropylaminocarbonylamino)pyrrolidine (11a)

To a solution of **10a** (1.4 g, 3.0 mmol) in a mixture of cyclohexene (0.54 mL, 17.3 mmol) and ethanol (30 mL) was added 10% Pd/C (850 mg). The suspension was refluxed for 15 min and then diluted with ethanol and filtered through Celite®. The solid was washed with ethanol and the combined filtrate and washings were concentrated to furnish **11a** as a brown solid, which was used without further purification due to the low stability of the product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.79–4.36 (m, 1H), 3.99–3.71 (m, 1H), 3.76–3.57 (dt, 6H), 3.42–3.28 (m, 2H), 3.08–3.02 (m, 2H), 2.52–2.11 (m, 2H), 1.49–1.33 (m, 2H), 1.13 (t, 9H), 0.64–0.50 (m, 2H); MS (EI): $m/z = 378.3$ (M+1, calcd. for M^+: 377.2, 406.2 (M^+ +2–23–18).

(2*S*,4*S*)-2-*tert*-Butylaminocarbonyl-4-(3-triethoxysilylpropylaminocarbonylamino)pyrrolidine (11b)

To a solution of **10b** (900 mg, 2.23 mmol) in a mixture of cyclohexene (10 mL, 9.86 mmol) and ethanol (15 mL) was added 10% Pd/C (400 mg). The suspension was refluxed during 1 h and then diluted with ethanol. After cooling at room temperature, the solution was filtered through Celite®, washed with ethanol and the solvent was removed under reduced pressure yielding **11b** quantitatively as a pale brown solid; yield: 958 mg (2.20 mmol). No purification was possible due to the instability of the product. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32–4.22 (m, 1H), 3.99–3.88 (m, 6H), 3.45–3.24 (m, 3H), 3.21–3.10 (m, 1H), 2.52–2.46 (m, 1H), 2.33–2.45 (m, 1H), 1.87–1.73 (m, 3H), 1.3 (s, 9H), 1.2 (t, 9H), 0.77 (t, 2H); MS (EI): $m/z = 432.3$ (M+1, calcd. for M^+: 431).

General Procedure for Preparation of Supported Catalysts

A proline derivative (**11a** or **11b**) (100 mg) bearing a triethoxysilyl group in toluene (10 mL) was added to a suspension of the inorganic support (1 g) in a mixture of toluene/water (20 mL/20 μL). The mixture was refluxed for 24 h. The solid was then filtered and washed with toluene to remove the remaining non-supported proline derivative. The pale solid was dried under vacuum. The loading (0.52 mmol/g) of the resulting catalyst was calculated by elemental analysis based on nitrogen. Anal. found: C 11.0, H 2.2, N 2.2%.

(2*S*4*S*)-1,2-Dibenzyloxycarbonyl-4-(3-*tert*-butylureido)pyrrolidine (12)

To a solution of **9a** (2.20 g, 6.21 mmol) in anhydrous CH_2Cl_2 (32 mL) was added *tert*-butyl isocyanate (208.89 g, 2.11 mmol). The reaction mixture was stirred under Ar at room temperature for 1 h. The solvent was evaporated and the residue was purified by column chromatography (hexane/AcOEt, 1:1) to furnish **12** as a white solid; yield: 610 mg (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 10H, Ph), 5.23–5.01 (m, 4H, OCH_2), 4.44–4.36 (m, 1H, H-4), 4.25–4.17 (m, 1H, H-2), 3.88–3.79 (m, 1H, $H5_B$-$H5_A$), 3.31–3.21 (m, 1H, $H5_B$-$H5_A$), 2.61–2.48 (m, 1H, $H2_B$-$H2_A$), 2.00–1.83 (m, 1H, $H2_B$-$CH2_A$), 1.23 (s, 9H, CH_3); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ = 174.1, 159.4, 156.5, 137.8, 137.1, 129.5, 129.3, 129.2, 129.1, 128.8, 68.3, 59.4, 53.5, 50.8, 50.1, 37.8, 29.7; MS (EI): $m/z = 476.8$ (M+23, calcd. for M^+: 453.2); anal. calcd. for $C_{25}H_{31}N_3O_4$: C 68.6, H 7.1, N 9.6%; found: C 68.7, H 7.4, N 9.5%.

(2*S*,4*S*)-2-Carboxy-4-(*tert*-butylureido)pyrrolidine (13)

To a solution of **12** (350 mg, 0.78 mmol) in a mixture of cyclohexene (0.29 mL, 4.35 mmol) and ethanol (13 mL) was added 10% Pd/C (223 mg). The suspension was refluxed during 15 min and then diluted with ethanol. After cooling at room temperature, the solution was filtered through Celite®, washed with ethanol and the solvent was removed under reduced pressure yielding **13** quantitatively as a white solid. No purification was possible due to the instability of the product. ^{1}H NMR (300 MHz, DMSO): δ = 4.87–4.85 (m, 1H, H-2), 4.52–4.47 (m, 1H, H-4), 4.4–4.2 (m, 3H, 3 NH), 4.03–3.99 (m, 1H, $\underline{H}5_B$-$H5_A$), 3.76–3.72 (m, 1H, $H5_B$-$\underline{H}5_A$), 3.14–2.84 (m, 2H, H-3), 1.95 (s, 9H, CH_3); ^{13}C NMR (75 MHz, DMSO): δ = 173.9, 159.4 , 61.4, 52.0, 50.8, 50.2, 41.2, 29.7; MS (EI): $m/z = 250.5$ (M+23, calcd. for M^+: 229.1); anal. calcd. for $C_{10}H_{19}N_3O_3$: C 52.3, H 8.3, N 18.3%; found: C 52.4, H 8.2, N 18.6%.

General Procedure for the Catalytic Asymmetric Aldol Reaction of Hydroxyacetone and Aldehydes using L-Proline at Room Temperature

Same as ref.[2b] Yields, d.r., and ee values are reported in Table 2.

General Procedure for the Catalytic Asymmetric Aldol Reaction of Hydroxyacetone and Aldehydes using MCM41-Pro at 90 °C

To a suspension of hydroxyacetone (1 mL) and Pro-MCM-41 (20% mol) in anhydrous DMSO or toluene (1.6 mL) was added the aldehyde (0.5 mmol). The reaction mixture was stirred at 90 °C for 24–72 h. Then the catalyst was filtered, and NH_4Cl (sat)/AcOEt was added to the filtrate. The layers were separated and the aqueous phase was extracted thoroughly with AcOEt. The combined organic phases were dried ($MgSO_4$), concentrated and purified by flash chromatography to afford the pure aldol product. Yields, reaction times, d.r. and ee values are reported in Table 2.

General Procedure for the Catalytic Asymmetric Aldol Reaction of Hydroxyacetone and Aldehydes using L-Proline Assisted by MW Heating

To a mixture of hydroxyacetone (0.25 mL), L-Pro (20% mol), and anhydrous DMSO or toluene (1 mL) was added the aldehyde (0.5 mmol). Intermittent irradiation was applied: cycles of 1 min under MW irradiation/2 min of magnetic stirring outside the oven. Then, NH_4Cl and AcOEt were added. The layers were separated and the aqueous phase was extracted thoroughly with AcOEt. The combined organic phases were dried ($MgSO_4$), concentrated and purified by flash chromatography to afford the pure aldol product. Yields, reaction times, d.r. and ee values are reported in Table 4.

General Procedure for the Catalytic Asymmetric Aldol Reaction of Hydroxyacetone and Aldehydes using MCM41-Pro Assisted by MW Heating

To a mixture of hydroxyacetone (1 mL), Pro-MCM-41 (20% mol), and anhydrous DMSO or toluene (1.6 mL) was added the aldehyde (0.5 mmol). Intermittent irradiation was applied: cycles of 1 min under MW irradiation/2 min of magnetic stirring outside the oven. Then the catalyst was filtered, and NH_4Cl (sat)/AcOEt was added to the filtrate. The layers were separated and the aqueous phase was extracted thoroughly with AcOEt. The combined organic phases were dried ($MgSO_4$), concentrated and purified by flash chromatography to afford the pure aldol product. Yields, reaction times, d.r. and ee values are reported in Table 4.

(3*S*,4*S*)-3,4-Dihydroxy-5-methylhexan-2-one (*anti*-22)

Column chromatography (hexane/AcOEt, 4:1) yielded a yellow oil. The spectral data (^1H and ^{13}C NMR) were identical to those previously reported.[2b]

(3S,4S)-4-Cyclohexyl-3,4-dihydroxybutan-2-one (*anti*-23)

Column chromatography (hexane/AcOEt, 3:1) yielded a yellow oil. The spectral data (^1H and ^{13}C NMR) were identical to those previously reported.[2b]

(3S,4S)-4-Phenyl-3,4-dihydroxybutan-2-one (*anti*-24)

Column chromatography (hexane/AcOEt, 3:1) yielded a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.4-7.2$ (m, 5H, Ph), 5.01 (d, 1H, $J_{H3,H4} = 4.5$ Hz, H-4), 4.47 (d, 1H, H-3), 1.96 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.1$, 139.4, 128.6, 128.2, 126.5, 81.48, 75.1, 27.9. MS (EI): $m/z = 203.0$ (M+23, (calcd. for M^+: 180.08); anal. calcd. for $C_{10}H_{12}O_3$: C 66.6, H 6.7%; found: C 66.7, H 6.9%; Rt (GC, method: 80 °C, 2 min, 5 °C/min): 15.3 min.

(3*S*,4*R*)-4-Phenyl-3,4-dihydroxybutan-2-one (*syn*-25)

^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.4-7.2$ (m, 5H, Ph), 5.01 (d, 1H, H-4), 4.40 (d, 1H, H-3), 1.96 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.1$, 140.4, 128.2, 128.2, 81.0, 74.2, 26.7; Rt (GC, method: 120 °C, 2 min, 5 °C/min): 15.4 min.

(3*S*,4*R*,5*S*,6*S*)-7-*O*-Benzyl-5,6-*O*-isopropylidene-3,4-dihydroxyheptan-2-one (*anti*-26)

Column chromatography (hexane/AcOEt, 5:1) yielded a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.4-7.2$ (m, 5H, Ph), 4.57 (s, 2H, CH_2Bn), 4.3–4.1 (m, 3H, H-3, H-5, H-6), 3.8–3.5 (m, 3H, H-4, H-7), 2.31 (s, 3H, CH_3), 1.44 and 1.41 (s, 6H, Ip); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.7$, 137.7, 128.5, 127.9, 127.8, 110.0, 78.4, 78.3, 75.7, 73.7, 70.3, 70.2, 27.8,27.2, 26.9; MS (EI): $m/ = 325.2$ (M+1, calcd. for M^+: 324.1), 347.0 (M+23); anal. calcd. for $C_{17}H_{24}O_6$: C 62.9, H 7.4%; found: C 63.3, H 7.8%; Rt (GC, method: 120 °C, 2 min, 5 °C/min): 16.0 min.

(3*S*,4*S*,5*S*,6*S*)-7-*O*-Benzyl-5,6-*O*-isopropylidene-3,4-dihydroxyhetan-2-one (*syn*-27)

^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.4-7.2$ (m, 5H, Ph), 4.57 (s, 2H, CH_2), 4.3–4.1 (m, 3H, H-3, H-5, H-6), 3.8–3.5 (m, 3H, H-4, H-7), 2.28 (s, 3H, CH_3), 1.44 and 1.41 (s, 6H, Ip); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.2$, 137.1, 128.6, 128.0, 127.9, 109.7, 78.5, 78.4, 75.7, 73.8, 70.3, 70.2, 27.1, 27.0, 25.5; Rt (GC, method: 120 °C, 2 min, 5 °C/min): 16.3 min.

(3*S*,4*S*,5*R*)-4-Azido-6-*O*-benzyl-3,4-dihydroxyhexan-2-one (anti-28)

Column chromatography (hexane/AcOEt, 2:1) yielded a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.4-7.2$ (m, 5H, Ph), 4.57 (s, 2H, OCH_2), 4.3–4.1 (m, 2H, H-3, H-4), 3.8–3.6 (m, 2H,CH_2), 3.7 (s, 1H, H-5), 2.19 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.5$, 137.3, 129.0, 128.9, 128.2, 77.8, 76.8, 74.0, 71.8, 61.1, 28.5; MS (EI): $m/z = 280.2$ (M+1, (calcd. for M^+: 279.12), 302.0 (M+23); anal. calcd. for $C_{13}H_{17}N_3O_4$: C 55.9, H 6.1, N 15.0%; found: C 55.9, H 6.3, N 14.8%. Rt (GC, method: 150 °C, 2 min, 5 °C/min): 14.2 min.

(3*S*,4*R*,5*R*)-4-Azido-6-*O*-benzyl-3,4-dihydroxyhexan-2-one (*syn*-29)

^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.4-7.2$ (m, 5H, Ph), 4.57 (s, 2H, OCH_2), 4.3–4.1 (m, H-3, H-4), 3.8–3.6 (m, 2H, CH_2), 3.7 (s, 1H, H-5), 2.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.4$, 136.64, 129.2, 128.5, 127.9, 76.7, 76.2,74.2, 71.3, 61.4, 28.1; Rt (GC, method: 150 °C, 2 min, 5 °C/min): 14.9 min.

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References

[1] a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, 1st edn., Wiley-VCH, Weinheim, **2005**.

[2] a) B. List, R. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; d) H. Gröger, J. Wilken, *Angew. Chem. Int. Ed.* **2001**, *40*, 529–532; e) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620–621; f) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2003**, *42*, 2785–2788; g) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152–2154; h) A. B. Nortrup, D. W. C. MacMillan, *Science*. **2004**, 1752–1755.

[3] a) S. V. Ley, M. Bolli, H. Martin, B. Hinzen, A-G. Gervois, B. Hall, *J. Chem. Soc. Perkin Trans. 1* **1998**, *15*, 2239–2242; b) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, Ai-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; c) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; d) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; e) P. Pihko, *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; f) C. Mitchell, A. Lobb, S. V. Ley, *Synlett* **2005**, 611–614; g) A. Hartikka, P. Arvidsson, *Tetrahedron Asymmetry* **2004**, *15*, 1831–1834; g) A. Berkessel, B. Koch, J. Lex, *Adv. Synth. Catal.* **2004**, *346*, 1141–1146.

[4] For a complete overview of heterogenized catalyst, see: a) R. A. Sheldon, H. van Bekkum, (Eds.), *Fine Chemicals through Heterogeneous Catalysis*, Wiley-VCH, Weinheim, **2001**; for examples of chiral catalysis, see: b) D. E. De Vos, F. J. Vankejecom, P. A. Jacobs (Eds.), *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, **2000**; for examples of MCM-41, see: c) J. Y. Ying, C. P. Mehnert, M. S. Wong, *Angew. Chem. Int. Ed.* **1999**, *38*, 56–77; d) A. Corma, *Chem. Rev.* **1997**, *97*, 2373–2419; e) V. Ayala, A. Corma, M. Iglesias, F. Sánchez, *J. Mol. Catal. A: Chem.*, *221*, **2004**, 201–208, and references cited therein; f) a proline covalently anchored onto MCM-41 was recently reported to be highly active for aldol reactions using acetone and aromatic activated aldehydes: D. Dhar, I. Eadham, S. Chandrasekaran, *Proc. Ind. Acad. Sci (Chem. Sci.)* **2003**, 365–372.

[5] a) A. Bastida, A. Fernández-Mayoralas, R. Gómez, F. Iradier, J. C. Carretero, E. García-Junceda, *Chem. Eur. J.* **2001**, 2390–2397; b) M. Carpintero, A. Bastida, E. García-Junceda, J. Jiménez-Barbero, A. Fernández-Mayoralas, *Eur. J. Org. Chem.* **2001**, 4127–4135.

[6] A. Corma, S. Iborra, I. Rodríguez, F. Sánchez, *J. Catal.* **2002**, *211*, 208–215.

[7] a) For a complete description of the theoretical basis, see: J. M. Seco, M. Marco, E. Quínoa, R. Riguera, *Org. Lett.* **2000**, *21*, 3261–3264; b) for a general review of assignments by NMR, see: J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17–117.

[8] P. W. Feit, *J. Med. Chem.* **1964**, *7*, 14–17.

