

ARTICLE

Asymmetric Direct Aldol Reaction Using Modified Hydroxyproline (Hyp) Derivatives**Lo'ay A. Al-Momani***Department of Chemistry, Tafila Technical University, Tafila, Jordan.**Received on: 17th Apr. 2018;**Accepted on: 16th Jul. 2018*

Abstract: Coupling of 4-hydroxy-*D* and *L*-prolines with *D*- and *L*-prolines as well *D*- and *L*-valines *via* esterification of the -OH group is carried out. The resulting diamino acid derivatives are purified and used as enantioselective catalysts. For a model reaction, an asymmetric aldol reaction of *p*-nitrobenzaldehyde with acetone is applied. The catalytic properties of the produced catalysts are investigated to determine the effect of the auxiliary amino acids (proline and valine) on the enantiomeric ratio (*er*). A virtually quantitative conversion into the aldol product with traces of dehydration product was observed. The prepared catalysts show enantiomeric ratio (*er*) values of 91: 9 % to 70: 30% of *R/S*-isomers. All reactions are carried out with 20 % mol of the catalyst.

Keywords: Enantiomeric ratio, Organocatalysis, Hydroxyproline, Asymmetric aldol reaction.

Introduction

L-Proline and its derivatives attract the attention of many research groups in organic synthesis and methodology developments^[1-6]. This is due to their important features and properties to catalyze asymmetric reactions^[7]. Many reasons justified their use as organocatalysts in a wide range of asymmetric organic reactions^[8]. These include their small size, good availability, rigidity and low price^[1,2,5,7-10]. The secondary amine moiety of the proteinogenic amino acid *L*-proline and its derivatives is responsible for the stereoselectivity of the asymmetric reaction^[11-16]. It is accepted and proven that they transfer the chirality through their ability to build up an enamine intermediate and the formation of H-bonding^[17-19]. Zn complexes of *L*-proline and some of its derivatives were studied and reported as catalysts for aldol reaction^[20-22].

The enzymatically prepared hydroxyprolines (Hyp's; *trans*-4-*L*-Hyp, *cis*-4-*L*-Hyp, *trans*-4-*D*-Hyp)^[23] were targeted for skeletal and

functional modifications in order to enhance and improve their catalytic behaviors (Figure 1). The etherification of the -OH group resulted in slight enhancement in the enantiomeric excess of aldol (*trans*-4-*L*-Hyp, *ee* = 57 %, *O*-*t*-Bu-*trans*-4-*L*-Hyp, *ee* = 69 %) and Michael reactions (*trans*-4-*L*-Hyp, *ee* < 5 %, *O*-*t*-Bu-*trans*-4-*L*-Hyp, *ee* = 19 %). However, it was not the case for the asymmetric Mannich reaction (*trans*-4-*L*-Hyp, *ee* = 75 %, *O*-*t*-Bu-*trans*-4-*L*-Hyp, *ee* = 27 %)^[24]. These observations encouraged us to introduce further modifications^[25-27]. For instance, Ferrocene mono- and dicarboxylic acids were coupled with Hyp's *via* esterification. *Trans*-4-*L*-Hyp coupled with ferrocene dicarboxylic acid resulted in the formation of the *R*-enantiomer of β -hydroxyketone **R-37**, while *trans*-3-*L*-Hyp gave an excess of *S*-**37** isomer. This indicates that the position of the -OH group in the Hyp can be a key target for the modifications^[26]. Dimerization of *trans*-4-*L*-Hyp and *cis*-4-*L*-

Hyp via esterification with diacid moieties of different lengths had a significant influence on the aldol reaction results. Dimers show enhancements in both conversion as well as enantioselectivities, (55 % *ee* for **trans-4-L-Hyp** and **cis-4-L-Hyp**; 84 % *ee* for the corresponding dimers)^[27]. We have used *Z*-protected hydroxyproline amino acids **1,2** and **5**.

They were coupled via esterification through their OH group on position four with the *Z*-protected amino acids **7–10**. This coupling introduced a new stereocenter into the catalyst, in an attempt to increase the reactivity as well as enantioselectivity of the chosen aldol reaction model.

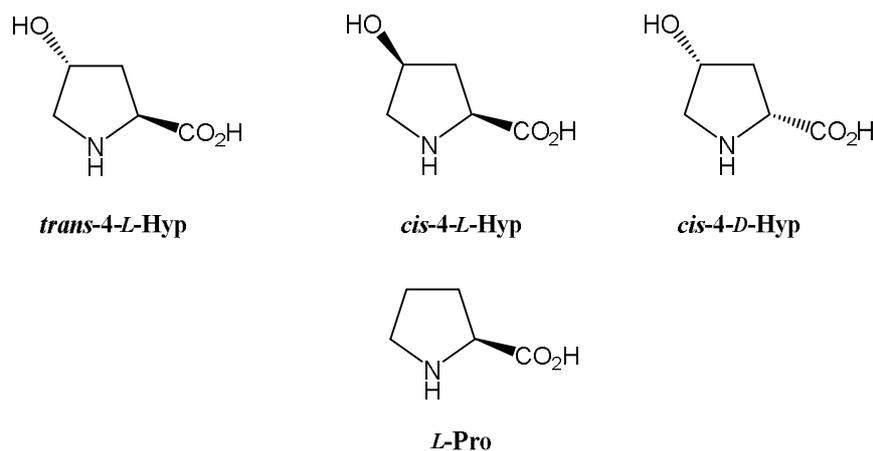


Figure 1. Proline and hydroxyprolines that were modified to catalysts **23–34**.

Experimental

General

All reagents were purchased and used without further treatment. Drying of solvents was achieved according to standard methods. Precoated TLC plates with silica gel (60F254) was provided by Merck. UV light of wavelength $\lambda=254$ nm was utilized to detect TLC spots. Column chromatography was carried out on silica gel 60 (Merck, 40–63 μm). NMR spectra were recorded on an AMX400 (Bruker BioSpin, Germany). The spectra were calibrated with: CDCl_3 ($\delta=7.26$ ppm), HDO ($\delta=4.81$ ppm) for ^1H -NMR, and for ^{13}C -NMR spectra with ^{13}C . CDCl_3 ($\delta=77.00$ ppm). HR-MS (CI) was carried out on a MAT95XL spectrometer. Infrared spectra (IR, neat) of the products were performed on Perkin Elmer FT-IR spectrometer. The determination of enantiomeric excess (*ee*) was determined by chiral phase HPLC (Chiral pak AS-H, Daicel). The eluent in the aldol reaction was *n*-hexane / isopropanol (70:30), UV = 254 nm, flow rate = 0.7 mL/min and T=25 °C. The retention time (t_R) for the *R*-isomer was 13.56 min, while that for the *S*-isomer was 17.35 min.

General Procedures (G)

Benzyl Esterification (General Procedure G1)^[27,28]

The free acids (**1**, **2** and **5**) (1.0 eq) were dissolved in 10 mL dry THF. After cooling to 0 °C, Triethylamine (2.0 eq) was poured to the solution. Benzyl bromide (1.5 eq) was dropped gradually to the mixture. The reaction was left to stir and warm up to RT overnight. After the completion of reaction, the solvent was evaporated and the residue was dissolved with ethyl acetate. The organic layer was washed with HCl (1 M, 20 mL), saturated NaHCO_3 solution (20 mL) and saturated brine solution (20 mL), respectively. The organic layer was evaporated to give a colorless oily product, which was purified using column chromatography to get the esters **3**, **4** and **6**.

Steglich Esterification (General Procedure G2)^[29]

The free acids (**7–10**) (1.0 eq.) were dissolved in DMF (5 mL). 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC, 2.5 eq.) and catalytic amount of 4-dimethylaminopyridine (DMAP, 0.2 eq.) were added. The mixture was cooled and stirred for 10

min at 0 °C. A CH₂Cl₂ (5 mL) solution of the alcohols (**3–5**) (2.0 eq.) was dropped to the mixture at 0 °C. The reaction mixture was stirred to warm up overnight. After completion, the reaction was diluted with 40 mL CH₂Cl₂ and washed successively with 10% citric acid solution, sat. NaHCO₃ solution and NaCl solution, respectively. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum. The residue was purified using column chromatography to get the diesters **11–22**.

Reductive deprotection of Z- and Bn- groups (General procedure G3)^[30, 31]

Z- and Bn-protected Hyp-derivatives (**11–22**) (1.0 eq.) were dissolved in dry MeOH (10 mL /100 mg). An amount of 20 % w/w of Pd/C was added to the reaction mixture. H₂ gas was purged into the reaction medium through a balloon. The reaction was followed by TLC. The product is very polar and UV invisible. The reaction was complete within 20 min. H₂O in equimolar amount to methanol was added to the mixture, which was subsequently filtered and the solvent evaporated to get the free amino acids (**23–34**).

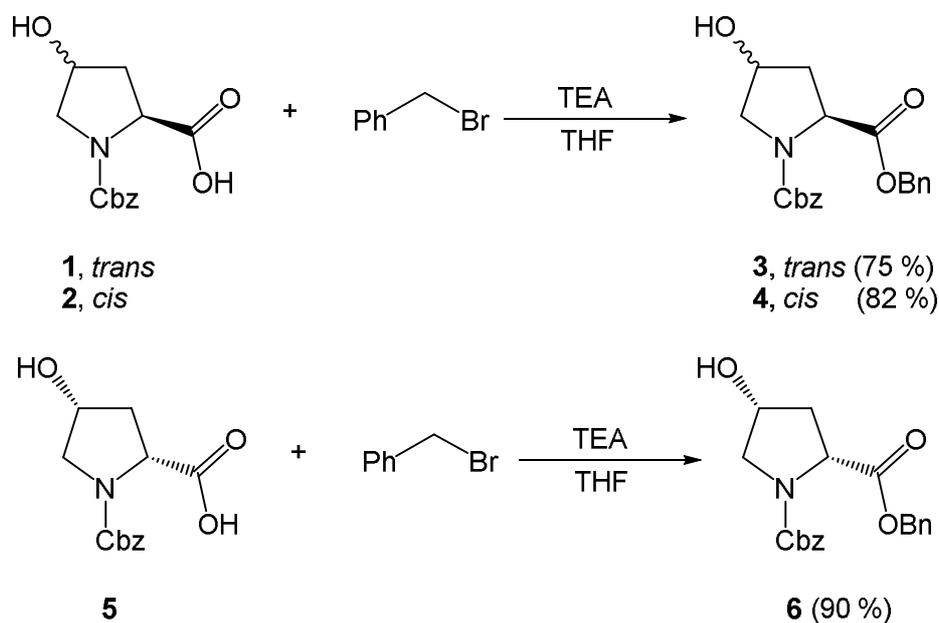
Aldol Reaction^[32]

p-Nitrobenzaldehyde (**35**) (151 mg, 1.0 mmol) was dissolved in 0.2 mL acetone (**36**). A solution of 0.2 mmol of catalysts **23–34** in 1.0 mL DMSO was added and the mixture was stirred overnight at RT. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organic layer (product **37**) was dried over anhydrous Na₂SO₄. ¹H-NMR (400

MHz, CDCl₃, 300 K, ppm): δ 8.21 (d, *J* = 8.8 Hz, 2H, H-*arom*), 7.54 (d, *J* = 8.6 Hz, 2H, H-*arom*), 5.26 (dt, *J* = 3.7 Hz, *J* = 7.6 Hz, 1H, CH-O), 3.58 (d, *J* = 3.3 Hz, 1H, C-OH), 2.85 (dd, *J* = 3.4 Hz, 6.1 Hz, 2H, CO-CH₂), 2.22 (s, 3H, CO-CH₃). ¹³C-NMR (101 MHz, CDCl₃, 300 K, ppm): δ 208.47 (C=O), 149.94 (C-*arom*), 147.26 (C-*arom*), 126.37 (C-*arom*), 123.72 (2 x C-*arom*), 68.86 (C-O), 51.46 (CO-CH₂), 30.68 (CO-CH₃).

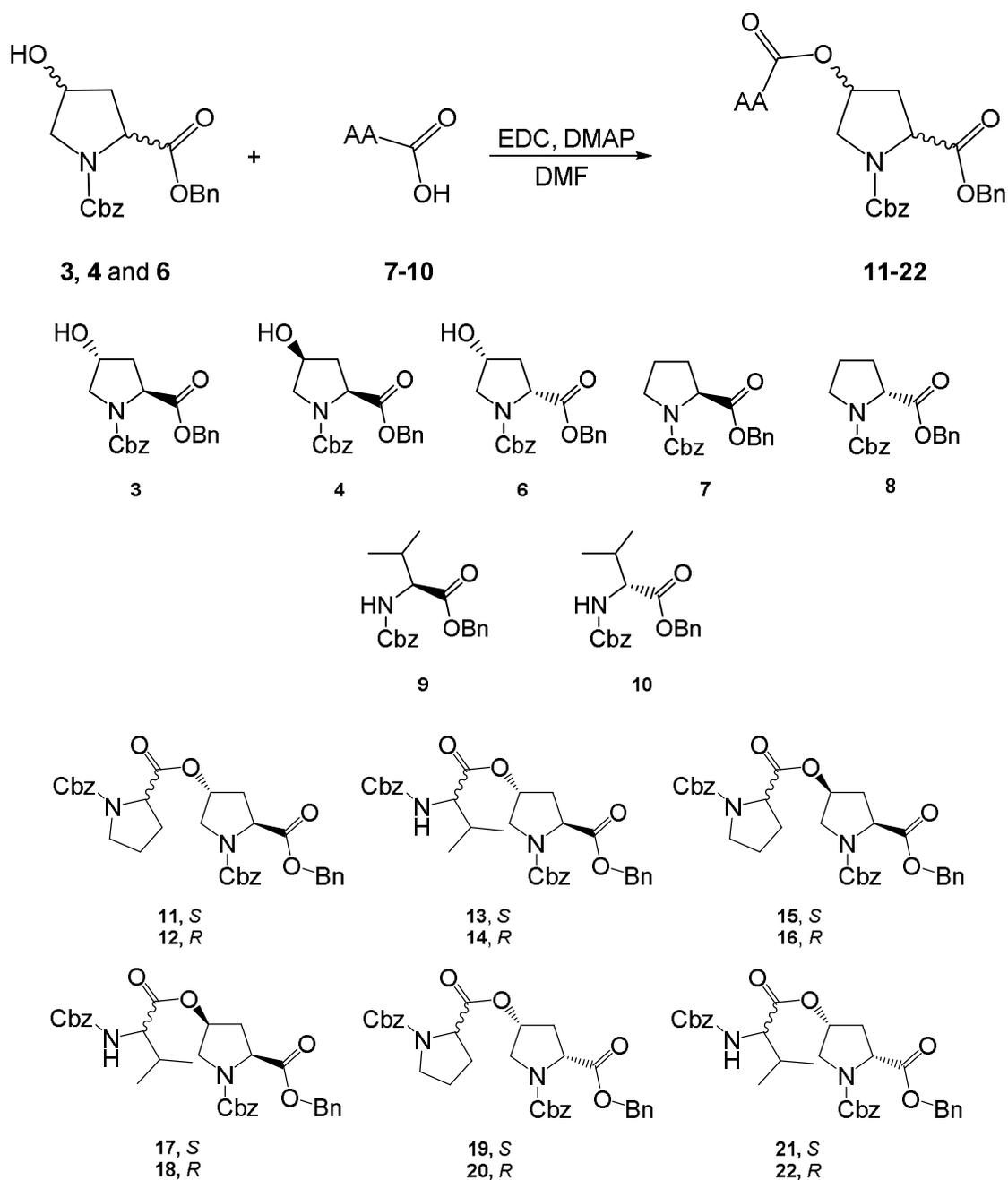
Results and Discussion

Hydroxyproline (Hyp) derivatives **1**, **2** and **5** were purchased with an N-terminal Cbz protection group and used without further purification. The derivatives **1**, **2** and **5** were esterified on their OH group (Scheme 1). Thus, the C-terminus was first protected as an ester. The protection as a benzyl ester (via the reaction of benzyl bromide in the presence of triethylamine (TEA), was chosen in order to simplify the deprotection step to generate the desired catalysts **23–34**. It is well established that both Cbz-O and BnO- groups will be deprotected simultaneously upon hydrogenation. All prepared -OBn Hyp (**3**, **4** and **6**) esters were purified over silica gel in very good yields of 75–90 %.

Scheme 1. C-terminal benzylation of the derivatives **1**, **2** and **5**^[27,28].

NMR, IR and high resolution mass (HR-MS) measurements were recorded for the benzyl esters. The number of ^{13}C -NMR peaks was more than expected, which may indicate the presence of several rotamers which resulted from the presence of the protective groups. The ^1H -NMR and the HR-MS proved high purity of the three prepared compounds (**3**, **4** and **6**). The IR-spectra showed characteristic peaks at about 3455 cm^{-1} for the alcoholic OH-group and ester stretching frequency at around 1740 cm^{-1} . The Steglich esterification was suggested to couple the Hyp derivatives **3**, **4** and **6** with the Cbz-N terminal protected *L*-proline (**7**), *D*-proline (**8**), *L*-valine (**9**) and *D*-valine (**10**) (Scheme 2). The reactions were performed overnight in solution

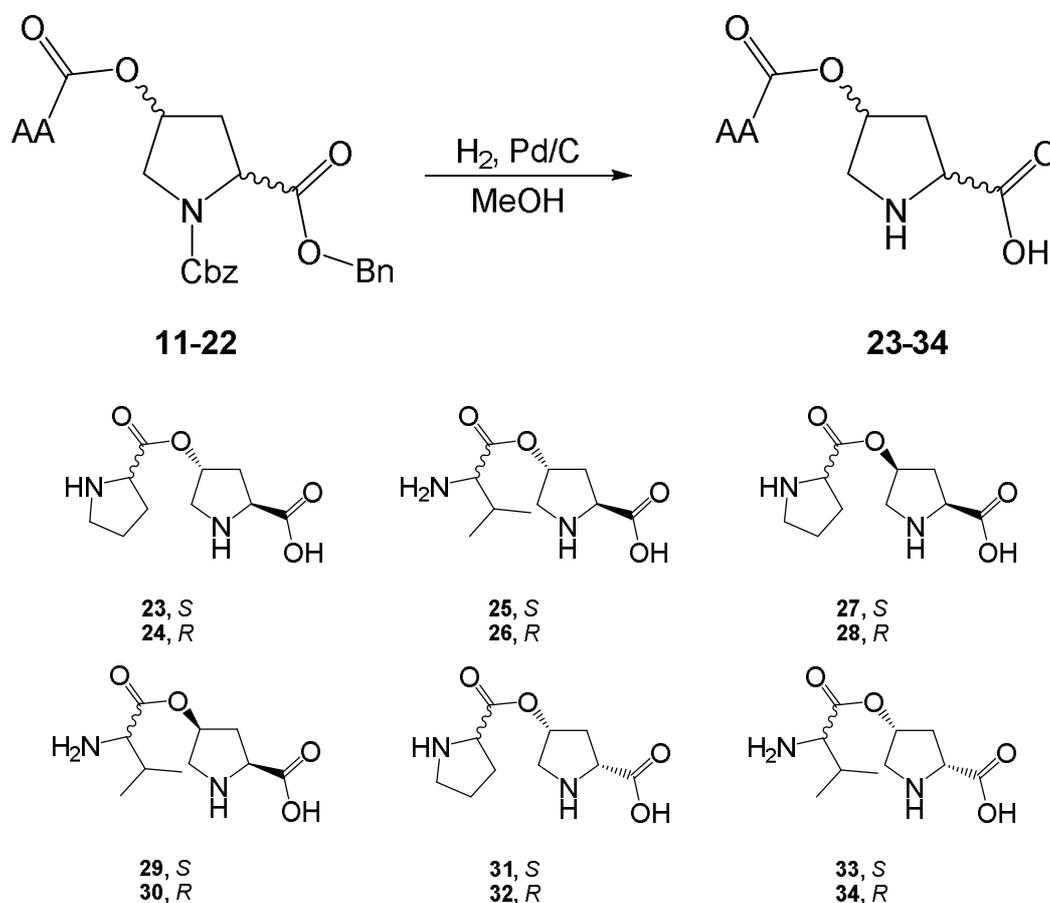
using mild coupling conditions, 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) in DMF. The products were purified by flash column chromatography to ensure their purity. The coupling reaction resulted in very good to excellent yields (73–97 %). NMR, IR and HR-MS for all compounds **11–22** were recorded. ^{13}C -NMR of compounds **11–22** showed more peaks than expected due to the presence of the rotamers mentioned before. The IR spectra of products **11–22** reveals the disappearance of the –OH groups stretching characteristic of compounds **3**, **4** and **6**, as well as the appearance of two carbonyl stretching frequencies at around 1740 and 1700 cm^{-1} .

Scheme 2. Steglich reaction and products of coupling amino acids 3, 4 and 6 with amino acids 7–10^[29].

Esters **11–22** were treated with H_2 in the presence of Pd/C in methanol (MeOH) for 30 minutes, in order to cleave the N-Cbz and O-Bn groups (Scheme 3).

1H -NMR of all deprotected products was recorded to check the purity of the compounds that should be used as catalysts. The yields were in the range of 70–98%.

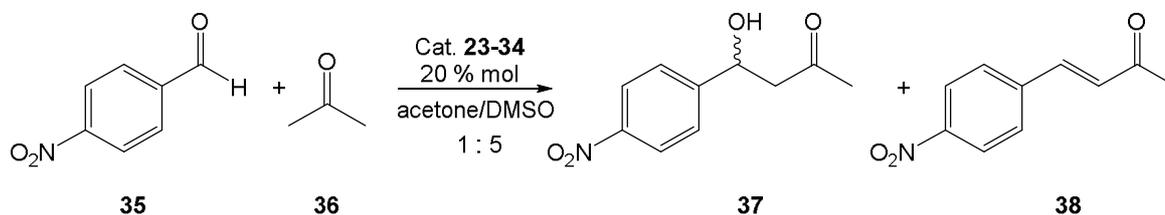
Scheme 3. Reductive cleavage of the N-Cbz and O-Bn in compounds 11–22 using H₂ and Pd/C in MeOH to yield catalysts 23–34^[30, 31].



Catalysts **23–34** were tested to conduct a model aldol reaction between 4-nitrobenzaldehyde (**35**) and acetone (**36**) in acetone/DMSO (1:5) solvent at room

temperature (rt) for 4 h and 24 h (Scheme 4). The catalysts **23–34** were used in 20 % mol ratio to compound **35**. This mol % was optimized in earlier works^[24–27].

Scheme 4. Aldol reaction between 4-nitrobenzaldehyde (35**) and acetone (**36**) in solvent mixture of acetone/DMSO (1:5)^[32].**



The conversion yield of each reaction for the aldol product β -hydroxyketone **37** was determined from the ¹H-NMR. The formation of

α,β -unsaturated ketone **38** in trace amounts was detected from ¹H-NMR as shown in Figure 2.

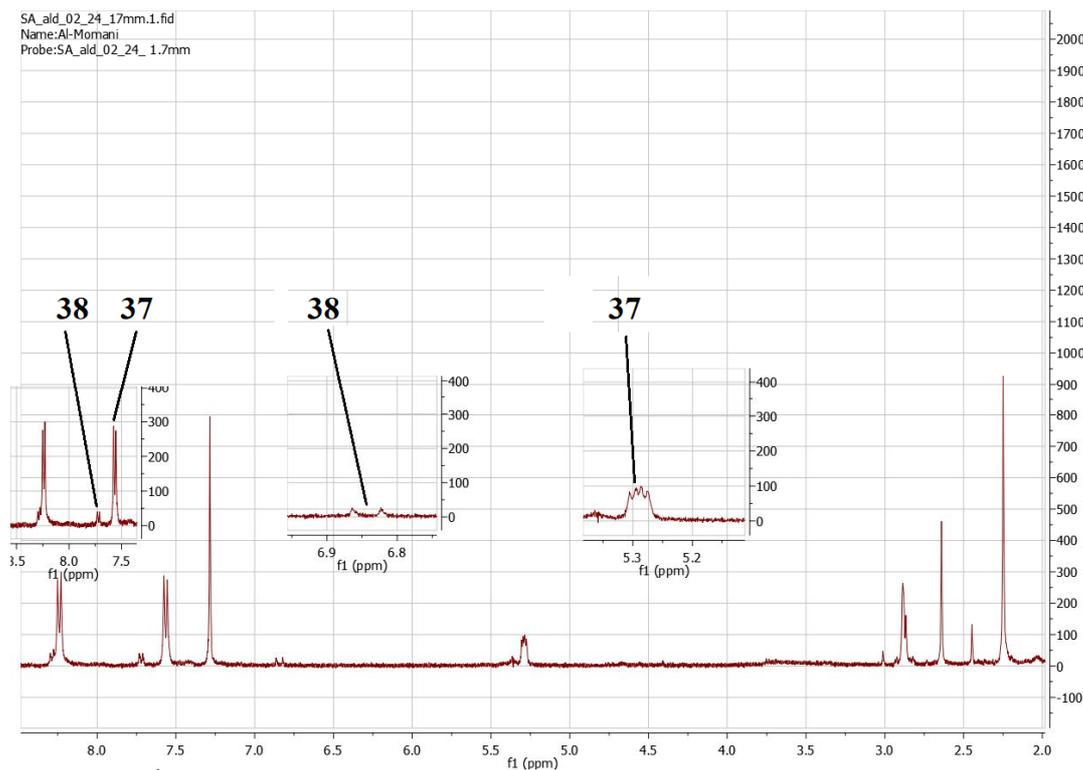


Figure 2. $^1\text{H-NMR}$ shows the formation of the aldol product **37** and the dehydration product **38**.

The determination of the enantiomeric ratio (*er*) was achieved using chiral phase HPLC column (Chiral pak AS-H, Daicel, Figure 3). The eluent for the aldol reaction was *n*-hexane/*iso*-propanol (70:30), UV = 254 nm, flow rate = 0.7 mL/min and T = 25 °C. The retention time (t_R) for the *R*-isomer was 13.56 min, while that for the *S*-isomer was 17.35 min (Figure 3). The aldol reaction depicted in scheme 4 shows high

reactivity with all modified catalysts **23–34**. All catalysts gave quantitative conversion of the aldehyde **35** into the aldol product **37** in just 4 h. This fact was supported by the disappearance of the aldehyde proton, which has the chemical shift at 10–11 ppm. Most of the catalysts show traces of the dehydration product **38**. The amount of the dehydration has not been determined (Figure 2).

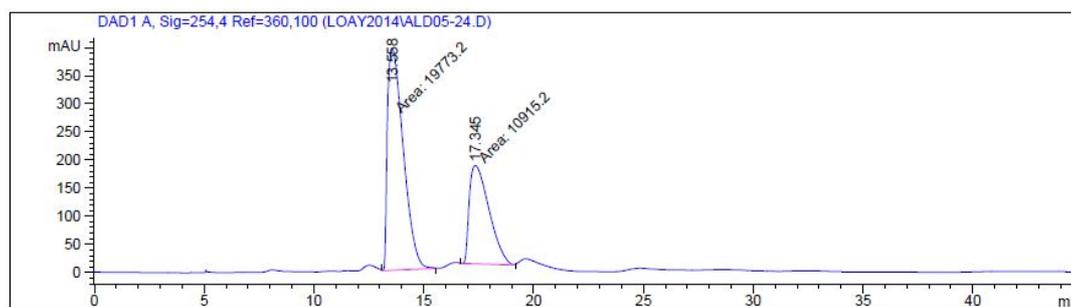


Figure 3. The chiral HPLC chromatogram of the *R*- and *S*-isomer of compound **37**.

Table 1 shows the results of the conversion as well as the enantiomeric ratio (*er*) of the catalysts **23–26**. It is worth noting that conversion ratios and *er* are not affected by the reaction time. All catalysts have the same main skeleton *trans*-4-*L*-Hyp-OH coupled via

esterification with *D*- and *L*-proline as well as with *D*- and *L*-valine. Herein, the main purpose is to study the factors that could affect the reactivities and the enantioselectivities of the Hyp derivatives as aldol catalysts. Therefore, all reaction conditions were kept fixed.

Table 1. Conversion and *er* % of model aldol reaction using catalysts 23–26.

Entry ^[a]	Catalyst ^[b]	Conversion % ^[c]	Time (4 h), <i>er</i> (R:S) ^[d]	Time (24 h), <i>er</i> (R:S) ^[d]
1	23	>98	77:23	77:23
2	24	>98	81:19	81:19
3	25	>98	91:09*	88:12*
4	26	>98	91:09*	90:10*
5 ²⁴	<i>L</i>-Pro	>95	NA	82.5:17.5
6 ²⁴	<i>trans-L</i>-Hyp	>95	NA	78.5:21.5
7 ²⁴	<i>cis-L</i>-Hyp	86	NA	77.5:22.5

^[a] Acetone/DMSO (1:5) as a solvent.

^[b] 20% mol.

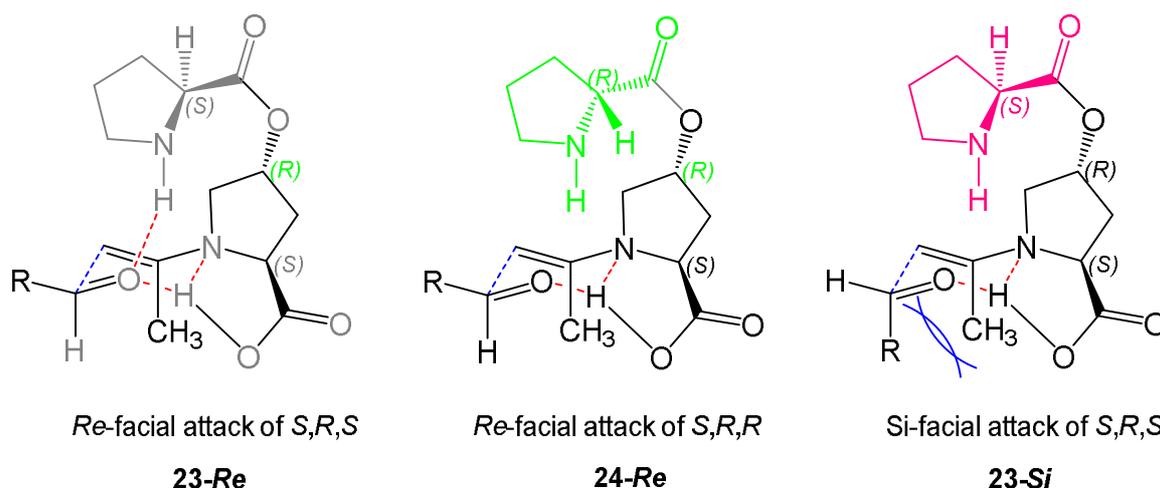
^[c] Determined by ¹H-NMR.

^[d] Determined by chiral HPLC. *Traces of dehydration product (**38**) were detected.

The main factors to be studied include: rigidity, free rotation of the joint proline and valine, steric effect and possible hydrogen bonding. Compounds **23–26** have shown the same reactivity toward the model aldol reaction.

Comparing the enantioselectivities of catalysts **23** and **24**, it was observed that the *er* % of **23** (77:23) is slightly lower than that observed in case of **24** (81:19).

Scheme 5. Six-membered ring transition states (TS_s) of the enamine-intermediate with the aldehyde. 23-*Re*, 24-*Re* are the favored TS_s and 23-*Si* is the disfavored TS^[32–34].



This difference in the *er* % might be attributed to the stereochemistry of the *L*-proline moiety in **23-*Re*** (gray), which reveals high rigidity, that leads to a hydrogen-bonding between The N-H of the *L*-proline moiety in **23-*Re*** (gray) and the C=O of the aldehyde (Scheme 5). This hydrogen-bond could disturb the *Re*-facial attack resulting in the *R*-/*S*-**23** of (77:23, *er* %). In contrast, *D*-proline moiety (green) is less likely to form the hydrogen-bond which enhances the formation of the six-

membered ring transition state **24-*Re***. The **23-*Si*** transition state is disfavored because of the steric effect of the R-group of the aldehyde and the CH₃-group of the enamine intermediate. *L*- and *D*-valine in catalysts **25** and **26**, respectively, show no influence on the enantiomeric ratio. The free rotation of the isopropyl-group in valine prevents the formation of H-bonds that could disturb the formation of the TS (Table 1, entries 3 and 4).

Table 2. Conversion and *er* % of model aldol reaction using catalysts 27–30.

Entry ^[a]	Catalyst ^[b]	Conversion % ^[c]	Time (4 h), <i>er</i> (R:S) ^[d]	Time (24 h) <i>er</i> (R:S) ^[d]
1	27	>98	85:15	84:16
2	28	>98	70:30*	64:36*
3	29	>98	86:14*	87:13*
4	30	>98	88:12*	90:10*
5 ^[24]	L-Pro	>95	NA	82.5:17.5
6 ^[24]	trans-L-Hyp	>95	NA	78.5:21.5
7 ^[24]	cis-L-Hyp	86	NA	77.5:22.5

^[a] Acetone/DMSO (1:5) as a solvent.

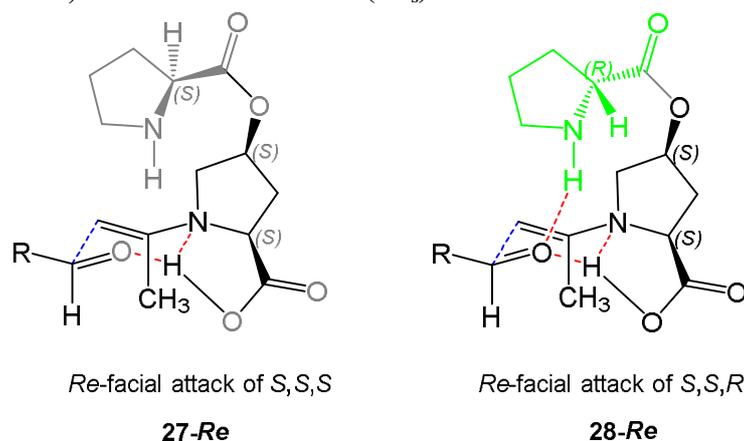
^[b] 20% mol.

^[c] Determined by ¹H-NMR.

^[d] Determined by chiral HPLC. *Traces of dehydration product (**38**) were detected.

In Table 2, catalyst **27** shows higher *er* % than in the case of **28**. These results is inconsistent with the results for **23** and **24**. Due to the inversed stereocenter at C-4 of Hyp, an H-bond can be formed between *D*-proline (green,

28-Re) moiety and the C=O, easier than the *L*-proline moiety (gray, **27-Re**) (Scheme 6). No effect of the stereochemistry of the valine moiety was observed on the stereoselectivities of catalysts **29** and **30** (Table 2, entries 3 and 4).

Scheme 6. Six-membered ring transition state (TS) of the enamine-intermediate with the aldehyde. 27-Re, 28-Re are the favored (TS_s)^[32–34].**Table 3. Conversion and *er* % of model aldol reaction using catalysts 31–34.**

Entry ^[a]	Catalyst ^[b]	Conversion % ^[c]	Time (4 h), <i>er</i> (R:S) % ^[d]	Time (24 h), <i>er</i> (R:S) % ^[d]
1	31	>98	33:67*	32:68*
2	32	>98	16:84*	16:84*
3	33	>98	14: 86 *	16:84*
4	34	>98	16:84	16:84

^[a] Acetone/DMSO (1:5) as a solvent.

^[b] 20% mol.

^[c] Determined by ¹H-NMR.

^[d] Determined by chiral HPLC. *Traces of dehydration product (**38**) were detected.

The results of catalysts **31–34** are summarized in Table 3. They show almost the opposite *er* % values of those shown in Table 1.

The only change is the stereochemistry on C-2 of the Hyp (Figure 4).

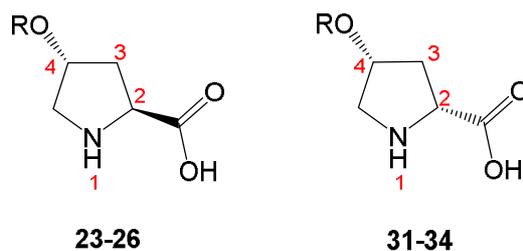
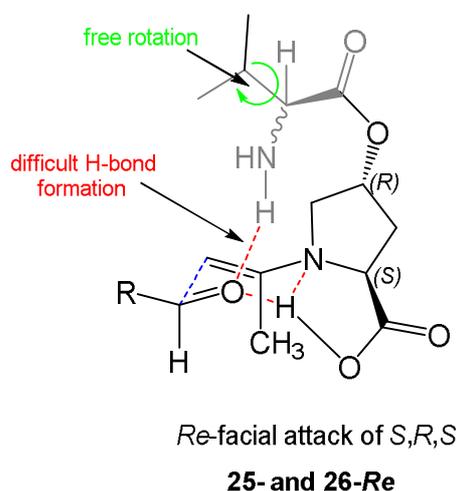


Figure 4. The difference in the stereochemistry on position 2 of Hyp derivatives **23–26** and **31–34**.

The most favored transition state while using the *D*-Hyp derivatives is the *Si*-facial attack TS (TS: Transition State). The *S*-isomer of the aldol reaction is the major stereoisomer. As a result, the *er* of the model aldol reaction can be controlled by the stereochemistry and the rigidity

of the amino acid joint to the Hyp. In the case of the proline (rigid), the stereoselectivity is enhanced if the Hyp α -position is opposite to that of the α -position proline moiety (entry 2, **24**, 82:18 (*R/S*), Table 1, and entry 1, **27**, 85:15 (*R/S*), Table 2).

Scheme 7. The six-membered ring transition state (TS) of the enamine-intermediate with the aldehyde. **25- and 26-Re** are the favored (TS_s)^[32–34].



In the case of valine moiety (Scheme 7), the stereochemistry of valine has no effect on the *er* % of the model aldol reaction, because of the suggested free rotation (see entries 3 and 4 in Table 1, Table 2 and Table 3).

Conclusions

Several factors were suggested to have significant effects on the enantioselectivity of the hydroxyproline derivative as asymmetric aldol reaction catalyst. They are namely; the steric factor, the rigidity and the ability to form hydrogen bonds. It is shown in the TS_s of **23-Re** and **24-Re** (Scheme 5) that the stereochemistry of the α -position of proline moiety opposes the configuration of the O-Hyp. The rigidity in proline moiety led to a proposal of H-bonding between the N-H of the proline moiety and the C=O of the aldehyde. This may disturb the

formation of the six-membered ring of the TS in the **23-Re** to give lower *er* % (77:23 (*R/S*), Table 1). In **24-Re**, the lack of H-bonding between the N-H of the proline and the C=O of the aldehyde enhances the formation of the six-membered ring of the TS_s, and enriches the *er* % (81:19 (*R/S*), Table 1). The same interpretation is used in the case of **27-Re** (*er* % = 84:16 (*R/S*), Table 2) and **28-Re** (*er* % = 64:36 (*R/S*), Table 2). The free rotation of the isopropyl group in the case of catalysts **25**, **26**, **29** and **30** may prevent the formation of H-Bond between N-H of valine moiety and the C=O of the aldehyde. Therefore, no effect of the stereochemistry of valine moiety was observed (**25**, *er* % = 88:12 (*R/S*), Table 1), (**26**, *er* % = 90:10 (*R/S*), Table 1), (**29**, *er* % = 87:13 (*R/S*), Table 2) and (**30**, *er* % = 90:10 (*R/S*), Table 2).

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