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RESEARCH ARTICLE

Aldol addition-cyclization reaction cascade on a platform of chiral Ni(II) complex of glycine schiff base

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Abstract: Using platform of a new type of chiral Ni(II) complex of glycine Schiff base we designed addition-cyclization reaction cascade to explore aspects of kinetic/thermodynamic formation of the corresponding (*S*)(2*S*,3*S*)/(*S*)(2*S*,3*R*) diastereomers. It was found that the final lactone products reflect the thermodynamic stereocontrol due to much greater rates of the reversible aldol addition vs. subsequent cyclization step. The observed 4/1 (*S*)(2*S*,3*S*)/(*S*)(2*S*,3*R*) diastereoselectivity in the reactions of new type of (*S*)-Ni(II) complexes constitute an improvement over the previously reported 1.7/1 ratio.

Keywords: asymmetric synthesis; aldol additions; tailor-made amino acids; Ni(II) complexes; Schiff bases; cascade/domino/tandem reaction.

Introduction

Tailor-made amino acids (AAs) [1] are in high demand in modern pharmaceutical industry. Along with fluorine [2], AAs' residues can be found in a growing number of marketed drugs and medicinal formulations [3]. The growing acceptance of peptides and modified peptides as drugs [4], strongly suggest that the pivotal role of tailor-made AAs in the design of pharmaceuticals will continue to increase [5]. Asymmetric synthesis of AAs is a mature science offering a plethora of various approaches [6]. Over the last decade, preparation of tailor-made AAs via Ni(II) complex intermediates (Scheme 1) has emerged as the most frequently used, methodologically dominant approach [7-8].

In this approach, chiral tridentate ligands 1 can be directly used in the reactions with racemic α- and β-AAs offering highly efficient deracemization, as well as (*S*)-to-(*R*) interconversion protocols [9-10]. In a more general version, chiral ligands **1** are transformed to Ni(II) complexes of glycine Schiff bases **2** by the reaction with glycine and source of Ni(II) ions. Compounds **2** are widely used as chiral nucleophilic glycine equivalents in the alkyl halide alkylations [11], Michael [12], Mannich [13], aldol [14] addition reactions, as well as various multi-step transformations [15]. Products **3** can be conveniently disassembled to release target AAs **4** along with the recovery and reuse of chiral ligands **1**. The overall process is economically and operationally attractive for large-scale asymmetric synthesis of tailor-made AAs [16]. Among the above-mentioned major pathways for homologation of the glycine moiety in complexes **2**, aldol addition, due to its inherent reversibility, is the most challenging approach (Scheme 2) [7b]. In this methodological work, using a new

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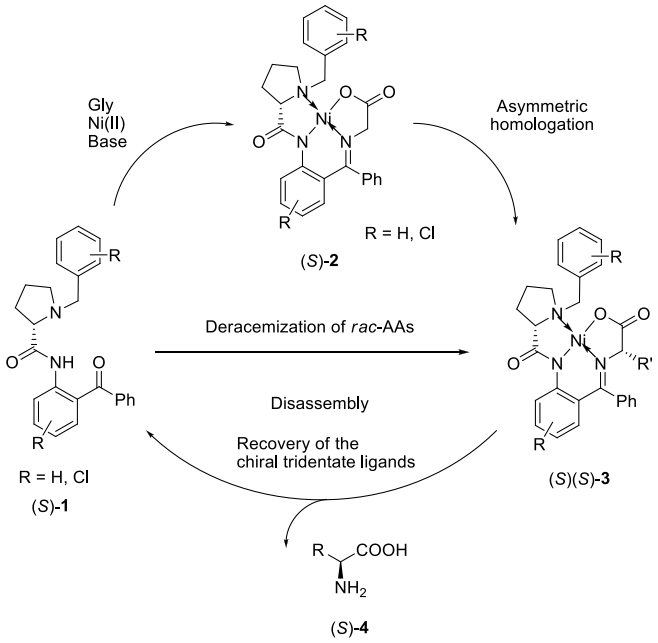
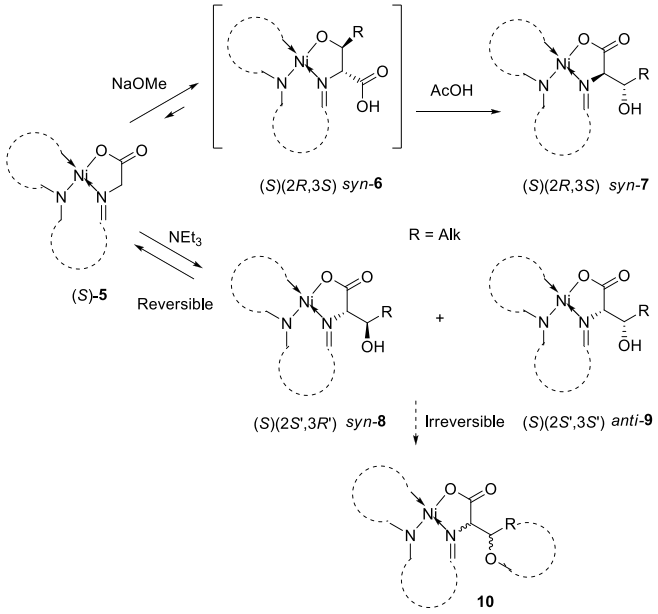
type of chiral ligands, we designed an aldol-cyclization reaction cascade in attempt to investigate the effect of the formation of irreversible final products on the overall stereochemical outcome of this reaction sequence. The results reported here expand our knowledge of Ni(II) complexes aldol reactivity and highlight noticeably greater stereocontrolling properties of new type of chiral tridentate ligands.

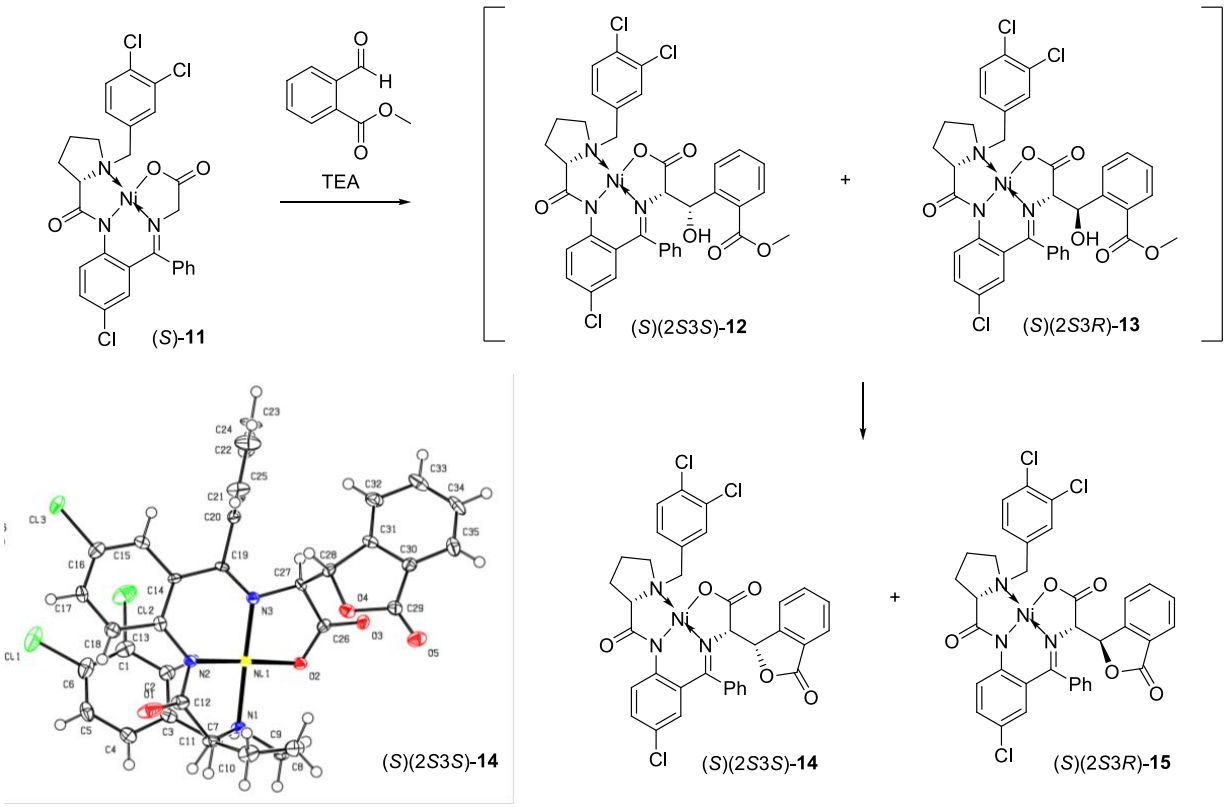


Scheme 1. Asymmetric synthesis of tailor-made amino acids via homologation of chiral glycine (*S*)-**1** Schiff base.



Scheme 2. General aspects of aldol addition reactions of Ni(II) complexes **5**; formation of reversible *syn*-**8** and *anti*-**9**, followed by cyclization to afford irreversible products **10**.

From the standpoint of mechanism and stereochemical outcome, aldol addition reactions of Ni(II) complexes of glycine Schiff bases have two distinct patterns (Scheme 2) depending on the reaction conditions. The first type of reactivity is observed in the presence of strong bases, such as alkoxides [17] or DBU [18]. In this case the reactions



Scheme 3. Aldol addition-cyclization reaction cascade; major (*S*)(2*S*,3*S*)-**14** and minor (*S*)(2*S*,3*R*)-**15** products and crystallographic structure of major diastereomer (*S*)(2*S*,3*S*)-**14**.

proceed with very high diastereoselectivity (> 90% de) and are virtually irreversible due to the *in situ* formation of hydroxy group-coordinated species **6**. Upon acidification of the reaction mixture, during work-up procedure, compounds **6** rearrange to a normal, carboxy group-coordinated complexes **7**. In the second option, under weakly basic conditions, such as catalyzed by triethylamine, aldol addition reactions are distinctively reversible with the equilibrium strongly favoring the starting compounds [19].

Consequently, the reactions usually require over 10-fold of the corresponding aldehyde to achieve a meaningful conversion of starting Ni(II) complexes **5**. Furthermore, under these reaction conditions the thermodynamically controlled diastereoselectivity (*syn*-**8** and *anti*-**9**) is quite low, ranging from 0 to 35% de. Considering these challenging inherent synthetic limitations, we were interested to know whether or not the stereochemical outcome can be improved when the aldol addition is followed by a transformation of reversible products *syn*-**8** and *anti*-**9** to irreversible derivatives **10**.

Results and Discussion

We posited that such process can be realized in addition-cyclization reaction cascade with in situ esterification of the key hydroxy group critical for the reverse aldol addition. As presented in Scheme 2, we selected methyl 2-formyl-benzoate, possessing well-positioned aldehyde and ester functionalities for the desired addition-cyclization cascade. As for the starting glycine Schiff base Ni(II) complex, we selected recently developed compound (*S*)-**11**, derived from strategically chloro-substituted ligand [20]. Complex (*S*)-**11** has never been used in the aldol additions but showed superior stereocontrolling properties in the alkyl halide alkylation [21] and deracemization of unprotected α- [22] and β-AAs [10].

After a series of preliminary experiments, we established that 6 equivalents of triethylamine, as a base, and 2 equivalents of methyl 2-formylbenzoate can be suitably used as the starting point in the investigation. As presented in Table 1, screening the reaction solvents, such as dichloromethane (entry1), acetone (entry 2), acetonitrile (entry 3) and methanol (entry 4) at ambient temperature gave more or less similar results in term of diastereoselectivity affording (*S*)(2*S*,3*S*)-complex **14** as the major reaction product. Diastereomers (*S*)(2*S*,3*S*)-**14** and (*S*)(2*S*,3*R*)-**15** were separated by column chromatography and fully characterized. Absolute configuration of major (*S*)(2*S*,3*S*)-**14** was established by single crystal X-ray analysis (Scheme 3 and SI). Absolute configuration of minor product (*S*)(2*S*,3*R*)-**15** was inferred based on its optical rotation ($[\alpha]^D$ = +1811.8), suggesting the (2*S*) stereochemistry and the (3*R*) by the deduction. No products with the (2*R*) absolute configuration, showing negative sign [19] of optical rotation, were found in the reaction mixture.

Considering entries 1-4, we concluded that the reaction solvent has virtually no effect on the diastereoselectivity of this aldol additions providing products (*S*)(2*S*,3*S*)-**14** and

Table 1. Optimization of reaction conditions[a].

Entry	Temp (°C)	Solvent	Ester (equiv)	Yield (%)	Dr[c]
1	rt	CH_2Cl_2	2.0	21	32:68
2	rt	aceton	2.0	16	28:72
3	rt	MeCN	2.0	12	34:66
4	rt	MeOH	2.0	53	37:63
5	-20	MeOH	2.0	66	64:36
6	0	MeOH	2.0	76	54:46
7	40	MeOH	2.0	58	25:75
8	60	MeOH	2.0	50	22:78
9	80	MeOH	2.0	45	19:81
10	40	MeOH	3.0	77	13:87
11	40	MeOH	5.0	93	20:80
12	40	MeOH	10.0	93	26:74
13[d]	40	MeOH	5.0	89	21:79
14[d]	40	MeOH	2.0	79	22:78

[a] Reaction conditions: *S*-CBPB **11** (0.1 mmol), methyl 2-formyl-benzoate, triethylamine (6 eq.), solvent (2.5 mL), 12 h;
[b] Isolated yield;
[c] Dr was determined by ^{1}H NMR;
[d] Ethyl 2-formylbenzoate was used.

(*S*)(2*S*,3*R*)-**15** in ratios between 28:72 and 37:63. By contrast, the chemical yields ranged much more prominently depending the reaction solvent (entry 3 vs. 4), suggesting methanol as an optimal choice (entry 4). Thus using menthol as a solvent, we explored the effect of the reaction temperature on the diastereoselectivity. Quite unexpectedly, the reaction of glycine Schiff base Ni(II) complex (*S*)-**2** with methyl 2-formylbenzoate conducted at -20 °C gave rise to the reverse diastereomeric preferences affording (*S*)(2*S*,3*R*)-**15** as a major product (entry 5). The same trend of the diastereoselectivity was still observed in the reaction conducted at 0 °C, albeit the preference for diastereomer (*S*)(2*S*,3*R*)-**15** was significantly reduced (entry 6). In sharp contrast the aldol addition performed at elevated temperature (40 °C, entry 7). Further increase of the reaction temperature to 60 °C (entry 8) and 80 °C (entry 9) led to gradual increase in (2*S*,3*S*) diastereoselectivity recording the diastereomeric ratios of 22:78 and 19:81, respectively. On the other hand, the chemical yield followed the opposite trend gradually decreasing from 76% (entry 6) to 45% (entry 9).

Based on these results, we concluded that the optimal temperature for these aldol reactions should be 40 °C (entry 7). It should be noted that the reactions were quite sluggish and the starting materials were never fully converted to products (*S*)(2*S*,3*S*)-**14** and (*S*)(2*S*,3*R*)-**15** within the standard 12 hours of the reaction time. Accordingly, we conducted series of reactions using greater than 2 equivalents excess of methyl 2-formylbenzoate. As presented in entries 10-12 the increase in the aldehyde stoichiometry allowed for noticeable improvement of the chemical yield to a respected 93% (entries 11, 12), suggesting 5 equivalents of the aldehyde as the optimal condition. Similar results were observed with application of

ethyl 2-formylbenzoate in the place of methyl 2-formylbenzoate (entries 13, 14).

Conclusions

In conclusion, in this methodological work we explored the triethylamine-catalyzed addition-cyclization reaction cascade between a new type of chiral Ni(II) complex of glycine Schiff and methyl/ethyl 2-formylbenzoates. The results obtained point to the thermodynamically controlled diastereoselectivity due to the much greater reaction rates of the reversible aldol additions vs. irreversible cyclizations. Nevertheless, the observed temperature-dependent oscillation of the stereochemical preferences, giving preference for (2*S*,3*R*) at low and (2*S*,3*S*) at elevated temperatures, was quite unexpected. Furthermore, the achieved 4/1 level of diastereoselectivity with over 90% chemical yields suggest synthetic potential of these reactions clearly deserving more comprehensive and focused investigation.

Experimental section

All the commercial reagents including solvents were used directly without further purification. All the experiments were monitored by thin layer chromatography (TLC) with UV light. The TLC employed 0.25 mm silica gel coated on glass plates. Column chromatography was performed with silica gel 60 (300-400 mesh). NMR spectra were recorded on Bruker 600 MHz spectrometers. Mass spectra (MS) were measured on Shimadzu LCMS-2020 with an etrospray ionization (ESI) probe operating in positive mode. Values of optical rotation were measured on Automatic Polarimeter SGW-531.

*General procedures for the reaction between methyl 2-formylbenzoate and (S)-**11***

Into a 10 mL vial were taken (*S*)-**11** (0.1 mmol), methyl 2-formylbenzoate (5 equiv), triethylamine (6 equiv), methanol (2.5 mL). The mixture was stirred at 40 °C for 12 h. Then the reaction was concentrated in vacuo. The residue was purified by column chromatography using DCM/EtOAc (1:1, v/v) as eluent to afford the desired product.

Compound (*S*)(2*S*3*S*)-**14**: red solid, mp 168-169 °C; $[\alpha]_D^{25}$ +2514.4 (c 0.09, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.99 (d, *J* 2.04 Hz, 1H), 8.14 (d, *J* 9.24 Hz, 1H), 7.88-7.86 (m, 1H), 7.80-7.79 (m, 1H), 7.77-7.74 (m, 1H), 7.72-7.69 (m, 1H), 7.60-7.57 (m, 1H), 7.54-7.48 (m, 2H), 7.45-7.43 (m, 1H), 7.41 (d, *J* 8.16 Hz, 1H), 7.19-7.17 (m, 1H), 7.10-7.08 (m, 1H), 6.73 (d, *J* 2.58 Hz, 1H), 6.40-6.39 (m, 1H), 5.29 (s, 1H), 4.51 (d, *J* 1.74 Hz, 1H), 4.27 (d, *J* 12.66 Hz, 1H), 4.19-4.11 (m, 1H), 3.61-3.58 (m, 1H), 3.41-3.38 (m, 1H), 3.21 (d, *J* 12.72 Hz, 1H), 2.94-2.88 (m, 1H), 2.68-2.60 (m, 1H), 2.31-2.27 (m, 1H), 2.12-2.06 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 180.5, 172.3, 171.4, 169.3, 145.2, 141.5, 135.2, 134.3, 133.8, 133.4, 133.2, 133.1, 132.9, 132.1, 131.0, 130.7, 130.1, 129.9, 129.8, 127.4, 127.1, 127.0, 125.9, 125.7, 125.5, 124.7, 121.6, 81.6, 72.8, 71.7, 63.0, 58.9, 31.3, 29.9, 23.2. MS (ESI) *m/z* Calcd. for $C_{35}H_{27}Cl_3N_3NiO_5^+$ $[M+H]^+$ 732.0. Found 732.0.

Compound (*S*)(2*S*3*R*)-**15**: red solid, mp 142-144 °C; $[\alpha]_D^{25}$ +1811.8 (c 0.06, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (d, *J* 2.04 Hz, 1H), 8.18 (d, *J* 9.36 Hz, 1H), 7.82-7.80 (m, 1H), 7.75-7.73 (m, 1H), 7.50-7.42 (m, 4H), 7.32 (d, *J* 8.22 Hz, 1H), 7.27-7.25 (m, 1H), 7.15-7.12 (m, 1H), 7.07-7.05 (m, 1H), 6.92-6.91 (m, 1H), 6.41 (d, *J* 2.58 Hz, 1H), 6.06 (d, *J* 3.84 Hz, 1H), 6.00-5.98 (m, 1H), 4.50 (d, *J* 3.9 Hz, 1H), 4.29 (d, *J* 12.6 Hz, 1H), 4.11-4.05 (m, 1H), 3.58-3.56 (m, 1H), 3.40-3.37 (m, 1H), 3.18-3.14 (m, 2H), 2.73-2.66 (m, 1H), 2.29-2.22 (m, 1H), 2.16-2.11 (m, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 179.8, 175.4, 172.4, 168.6, 144.9, 141.7, 135.2, 134.5, 133.6, 133.4, 133.3, 132.9, 132.8, 132.3, 131.1, 130.2, 129.8, 129.7, 129.6, 129.2, 128.8, 127.2, 127.1, 125.9, 125.8, 125.4, 123.5, 123.4, 80.5, 72.1, 71.8, 63.3, 58.9, 30.6, 29.7, 23.3. MS (ESI) *m/z* Calcd. for $C_{35}H_{27}Cl_3N_3NiO_5^+$ $[M+H]^+$ 732.0. Found 732.7.

Notes

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Author contributions. **Yupiao Zou, Zizhen Yin**: Synthesis of compounds, Investigation, Formal analysis, writing experimental section. **Haibo Mei, Hiroyuki Konno**: Investigation, Formal analysis, writing most of the manuscript. **Hiroki Moriwaki, Vadim A. Soloshonok and Jianlin Han**: Conceptualization, Supervision, Writing - review & editing. **Zizhen Yin**: X-ray analysis.

Supporting information

The characterization data, NMR spectra and single crystal for **14**.

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Каскадні реакції альдольного приєднання та циклізації на основі хірального комплексу Ni(II) основи Шифа гліцину

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Резюме: На базі хірального комплексу Ni(II) основи Шифа гліцину нового типу було розроблено каскадні реакції приєднання-циклізації з метою вивчення аспектів кінетичного/термодинамічного утворення відповідних (*S*)(2*S*,3*S*)/(*S*)(2*S*,3*R*) діастереомерів. Було знайдено, що утворені лактони в значній мірі є продуктами термодинамічно контрольованої діастереоселективності завдяки значному внеску зворотньої реакції альдольного приєднання порівняно із подальшою циклізацією. Досить несподіваним виявився факт температурної залежності стереохімічних співвідношень продуктів реакції: при низькій температурі утворювався переважно (2*S*,3*R*) діастереомер, у той час як при підвищеній – (2*S*,3*S*). Спостережувана діастереоселективність становила 4/1 (*S*)(2*S*,3*S*)/(*S*)(2*S*,3*R*), що є значно кращим показником порівняно із попередніми даними (1.7/1). Подібний рівень діастереоселективності, а також сумарний вихід продуктів реакції (більш ніж 90%), свідчать про великий синтетичний потенціал даного методу, що однозначно заслуговує на всебічне та цілеспрямоване дослідження.

Ключові слова: асиметричний синтез; альдольне приєднання; специфічні неприродні амінокислоти; Ni(II) комплекси; основи Шифа; каскадні/доміно/тандемні реакції.