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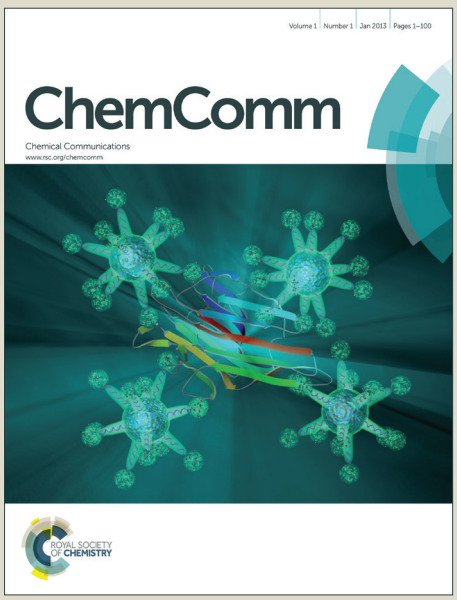

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Asymmetric synthesis of α-(1-oxoisoindolin-3-yl)glycine: Synthetic and mechanistic challenges†

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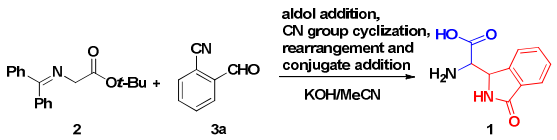
We report herein that the NaOMe-catalyzed reactions between chiral glycine Schiff base (*S*)-4 with 2-cyanobenzaldehyde 3a provide for a convenient preparation of novel α-(1-oxoisoindolin-3-yl)glycine 1 of high pharmaceutical potential. The reactions involve at least eight synthetic steps and mechanistically can be realized only with application of Ni(II) complexes described in this study.

α-Amino acids are the building blocks of peptides and proteins which critically influence all vital processes of human and animal biology. One of the central objectives in modern chemistry and medicine is to obtain in-depth understanding of peptides three-dimensional structure and its relationship to biological activity as the physiological basis of human health.[1] In this regard, tailor-made amino acids play a paramount role allowing for some rational control over peptide conformations and therefore biological properties.[2] Among numerous α,β-diamino acids,[3] of particular importance are β-cyclized α,β-diamino acids which were shown to limit the number of peptide side-chain conformations, the most exigent aspect in the *de novo* peptide design.[2,4] Consistent with our interest in the asymmetric synthesis of tailor-made amino acids,[5] we were excited to notice a recent contribution by Massa et al. introducing a novel type of α,β-diamino acids fused with important heterocyclic nuclei, such as α-(1-oxoisoindolin-3-yl)glycine **1**[6] (Scheme 1). Massa's group has proposed an elegant synthetic approach starting from O'Donnell Schiff base **2**[7] and 2-cyanobenzaldehyde **3a**.

This reaction presents a very synthetically fascinating cascade of *in situ* transformations including aldol addition, CN group cyclization, rearrangement and conjugate addition. Drawing inspiration from these results, we decided to explore



Scheme 1. Massa's group approach to α-(1-oxoisoindolin-3-yl)glycine **1**.

an alternative method for the asymmetric synthesis of amino acid **1** using chiral Ni(II) complexes of glycine Schiff base.[8] We report herein our preliminary results on this project demonstrating selective preparation of one out of four theoretically possible enantiomers of amino acid **1** as well as mechanistically complicated and rather unexpected stereochemical outcome observed in this study.

Chiral Ni(II) complex (*S*)-**4** (Table 1) is a commercially available, inexpensive and well studied nucleophilic glycine equivalent.[8,9] It is substantially more stable, as compared to O'Donnell Schiff base **2** and can be used for relatively large scale asymmetric synthesis[10] of α-amino acids. On the other hand aldol addition reactions[11] of complex (*S*)-**4** with aromatic aldehydes have been one of the least successful areas of Schiff base (*S*)-**4** chemistry. Under the conditions of kinetic control, these reactions were shown to be highly reversible and resulting in the formation of all four theoretically possible diastereomeric products.[8b]

Quite similarly to this general trend, initial efforts to react glycine Schiff base (*S*)-**4** with aldehyde **3a** gave a mixture of diastereomeric products **A**-**D** (Table 1). All four diastereomers, and their chemical composition (mass), can be clearly detected by LC-MS (see ESI file) and were labeled **A**-**D** according to the increasing retention times. The diastereomer **D** was easily isolated in diastereomerically pure form and full characterization. Taking advantage of its high crystallinity, we were able to perform a crystallographic analysis which revealed the (2*R*,3*S*) absolute configuration of product **5a** (**D**).[12]

With these experimental data in hand, we conducted a systematic study of this reaction to optimize possibly some selective formation of one major diastereomeric product. The key results are presented in Table 1.

First of all, after extensive experimentation, we have determined that application of methanol as a solvent and NaOMe as a base allows for optimal reaction rates and

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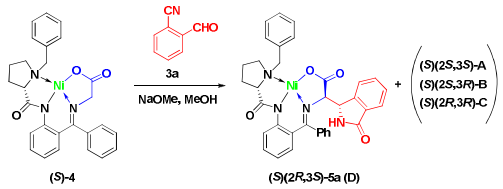
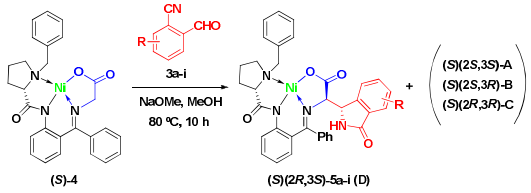
Table 1. Optimization of the reaction conditions between (*S*)-**4** with aldehyde **3a**.[a]



Entry	Time (h)	Temp (ºC)	Yield (%)[b]	dr (A/B/C/D)[c]
1	20	r.t.	80.3	58/22/0/20
2	20	40	71.1	19/5/1/75
3	16	60	68.9	5/2/8/85
4	0.5	80	84.7	45/18/3/34
5	10	80	62.4	6/1/0/93
6	15	80	62.4	6/1/0/93

[a] Reaction conditions: (*S*)-**4** (0.2 mmol), **3a** (0.22 mmol), sodium methoxide (0.24 mmol), methanol (2 mL). [b] Combined yield of isolated crude products **A**-**D**. [c] Determined by LC/MS analysis on the crude reaction mixtures.

Table 2. Investigation of the substrate generality.[a]



Entry	R	(*S*)(2*R*,3*S*)-**5**	Yield (%)[b]	dr (A/B/C/D)[c]
1	H	**5a**	62.4	6/1/0/93
2	4-F	**5b**	44.8	5/1/0/94
3	5-F	**5c**	32.3	1/5/0/94
4	4-Br	**5d**	24.7	6/1/0/93
5	4-MeO	**5e**	70.1	5/2/0/93
6	4-Me	**5f**	66.4	6/2/0/92
7	5-MeO	**5g**	60.1	6/1/0/93
8	4,5-diMeO	**5h**	70.8	5/2/0/92
9	4,5-methylenedioxy	**5i**	69.0	5/1/0/94

[a] Reactions conditions: (*S*)-**4** (0.2 mmol), **3a-i** (0.22 mmol) and sodium methoxide (0.24 mmol), methanol (2 mL), 80 ºC, 10 h. [b] Combined yield of isolated products **A**-**D**. [c] Determined by LC/MS analysis on the crude reaction mixtures.

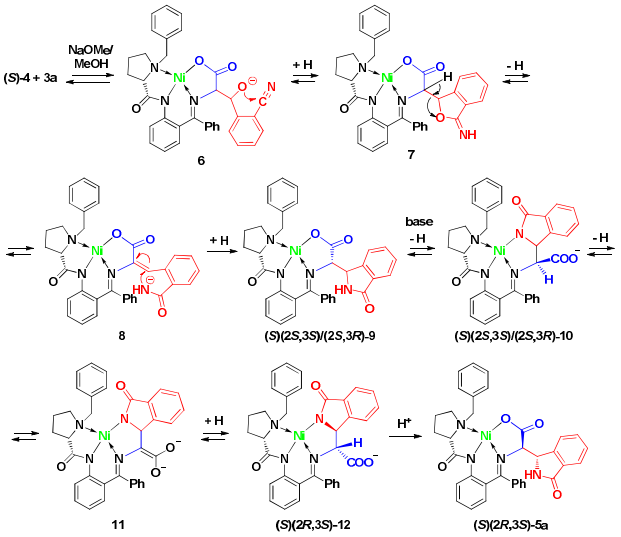
complete conversion of the starting Schiff base (*S*)-**4** using just 1.1 equivalent of aldehyde **3a**. Second, the reaction takes place readily and quite cleanly at ambient temperature giving rise to a mixture of diastereomers in reasonably good chemical yield (Table 1, Entry 1). Finally, the stereochemical outcome observed on the initial reaction stage is, most likely, kinetically controlled, as it was found to depend on the reaction time and temperature. These significant observations prompted us to focus on the temperature as a key factor in optimizing the reaction stereochemical outcome. As one can see in the reaction conducted at ambient temperature (Entry 1) the diastereomer **A** was noticeably major with minors **B** and **D** obtained and nearly equal amounts. In sharp contrast, performing the reaction at 40 ºC Entry 2) led to a dramatic change in relative ratios of diastereomers, the diastereomer (2*R*,3*S*)-**5a** (**D**) was produced as the major product while relative amounts of **A** and **B** were significantly reduced. Further increase of the reaction temperature to 60 ºC (Entry 3) afforded the diastereomer (2*R*,3*S*)-**5a** (**D**) with meaningful selectivity over the stereoisomers **A**-**C**. On the other hand, the increase of the reaction temperature resulted in gradual decrease in the chemical yield of the reaction products (Entries 1-3). Our final efforts in optimization of the reaction conditions are presented in entries 4-6. This additional set of experiments allowed us to determine that the final thermodynamic control can be reached at 80 ºC within 10 h (Entry 4 vs. 5 and 5 vs. 6) affording the major diastereomer (2*R*,3*S*)-**5a** (**D**) in synthetically useful chemical yield.

To follow up on these successful results, we decided to evaluate generality of this procedure with various 2-cyanobenzaldehydes . The results are presented in Table 2. All reactions were conducted under the standard conditions(see ESI file). In all cases the stereochemical outcome was virtually the same (Table 2, Entries 2-9) favoring the (*S*)(2*R*,3*S*) configured products **5b-i** (**D**) as major thermodynamic products. Benzaldehydes **3b-d**, containing halogen atom, gave complexes **5b-d** with noticeably lower yields (Entries 2-4 vs. 1) while the electron-donating group substituted **3e-3i** afforded major diastereomer **5e-5i** in good yields (60%-71%, Entries 5-9). This brief substrate generality study suggested that the presence of electron-withdrawing/donating substituents on the starting benzaldehydes **3** has no effect on the thermodynamically controlled diastereoselectivity in these reactions. On the other hand, the substituents might influence the reactivity of derivatives **3b-d** implying that the reaction conditions should be further optimized if a particular, for example fluorine-containing,[13] structural derivative is needed.

With results in hand, we were in position to discuss mechanistic aspects of the reactions under study. Scheme 2 details our proposed rationale for the observed stereochemical outcome.

Based on the mechanism established by Massa's group,[6] one can assume that the initial reaction step results in the formation of expected aldol product **6**. Ionized form of **6** would undergo cyclization with the *o*-CN group to afford intermediate compound **7** which further undergoes rearrangement to give ionized amide derivative **8**. Intramolecular conjugate addition in **8** would give rise to products **9**. Presumably, the formation of derivatives **9** is the rate determining and irreversible step.

It is well-established that homologation of Ni(II) complex of Schiff base (*S*)-**4** via alkylations,[8a,14] Michael[15] and Mannich[8b] type reactions, strongly favors α-(*S*) stereochemistry of the corresponding products. In the aldol reactions of (*S*)-**4**, under kinetic control, the same α-(*S*) absolute configuration of the addition products was shown to be greatly preferred.[8b,11] Therefore it is quite reasonable to assume that the major diastereomer **A**, as well as **B** in the mixture **9** are of α-(*S*) configuration. Further epimerization of **A** and **B** diastereomers to the final product (2*R*,3*S*)-**5** can be accounted for the following chain of transformations.[8b] As one may agree, in the presence of NaOMe, the amide NH in compounds **9** can be easily ionized and substitute the carboxy group in the Ni(II) coordination plane, giving rise to



Scheme 2. Proposed rationale for the formation and absolute configuration of product (*S*)(2*R*,3*S*)-**5a**.

intermediates **10**. In compounds **10** the carboxy group is up, relatively to the Ni(II) coordination plane, which is sterically strongly unfavorable position.[16] Therefore, it will undergo α-epimerization, via enolate **11**, to form more thermodynamically stable intermediate **12** with carboxy group pointing down and α-stereogenic carbon of the (*R*) configuration. The most stable relative stereochemistry of α- and β-carbons is *trans* rendering the intermediates **12** of (*S*)(2*R*,3*S*) absolute configuration. The acidic work-up, and protonation of compound **12** leads to its rearrangement into normal, carboxy-coordinated structure (*S*)(2*R*,3*S*)-**5a**.[17]

One may agree that the chain of transformations described here cannot be realized in the case of O'Donnell's Schiff base **2** (Scheme 1) and is a distinguishing feature of Ni(II) complex chemistry allowing for the observed synthetically useful thermodynamically controlled stereochemical outcome.

As a final goal of this preliminary study, we decided to demonstrate the preparation of the target free α-(1-oxoisoindolin-3-yl)glycine **1**. Product (2*R*,3*S*)-**5a** was isolated in diastereomerically pure form on 1 g scale by column chromatography and disassembled under the standard conditions, using 1 *N* HCl, to furnish free amino acid (2*R*,3*S*)-**1** (see ESI file) in 82.5% yield. Along with amino acid (2*R*,3*S*)-**1**, chiral ligand (*S*)-**13** was recycled with 82% yield and used for preparation of starting glycine Schiff base (*S*)-**4**.

In conclusion, this research has demonstrated that the reaction of chiral glycine Schiff base (*S*)-**4** with 2-cyanobenzaldehyde **3**, conducted in the presence of NaOMe, can be a reliable approach for the asymmetric preparation of chiral α-(1-oxoisoindolin-3-yl)glycine **1** of high pharmaceutical potential. Synthetically and mechanistically, this reaction is unusually complex involving cascade of transformations on the stages of structure formation and thermodynamically controlled diastereoselectivity. It should be emphasized that the stereochemical outcome obtained can be realized only with application of used in this work Ni(II) complexes and not with any other types of nucleophilic glycine equivalents. Considering the fact that the whole process requires at least 8 synthetic steps, the achieved yields of >60% and 93% selectivity are rather notable and practically useful.

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16 The position of carboxy group up, relatively to the Ni(II) coordination plane, is stereochemically equivalent to α-(*R*) configuration of α-mono-substituted derivatives and is strongly sterically disfavored by the chiral environment of the Ni(II) complex, see: ref. 8b.

17 The pure isomer **5a** (**A**) was isolated and the crystallographic analysis revealed the (2*S*,3*S*) absolute configuration of **5a (A)**. CCDC 1031123 contains the supplementary crystallographic data for this paper. The transformation of **5a** (**A**) to **5a** (**D**) was clearly observed under standard reaction conditions. (detailed information see ESI file).