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Asymmetric Synthesis of α-Amino Acids under Operationally Convenient Conditions

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Dedicated to Professor Yuri Nikolaevich Belokon on the occasion of his 75th birthday.

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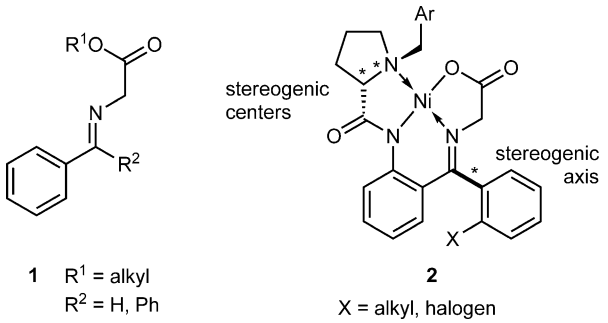
Abstract: A new multipurpose glycine equivalent for the general asymmetric synthesis of α-amino acids is introduced. The chiral reagent can be transformed to various amino acids by alkylations with alkyl halides as well as aldol and Michael addition reactions under operationally convenient reaction conditions at room temperature with virtually complete stereochemical control.

Keywords: amino acids; asymmetric synthesis; central and axial chirality; nickel; Schiff bases

α-Amino acids (α-AAs) can be found in nature as structural units of peptides and proteins leading to countless biological functions in living beings.[1] Consequently, the search for efficient asymmetric syntheses of α-AAs has always been a goal of paramount importance for synthetic chemists. The wealth of methodology available to date for accessing α-AAs features true synthetic ingenuity allowing the preparation of virtually any tailor-made[2] structurally/functionally complex α-AA.[3,4] Methods include stoichiometric as well as catalytic approaches.[1,3–5] Some, such as the asymmetric hydrogenation of dehydroamino acid derivatives utilizing rhodium- or ruthenium-based catalytic systems, have already been applied on (multi-)kilogram scales.[6,7] Aspects of practicality and cost, however, have often been neglected rendering the known chemical methods prohibitively expensive as compared to their enzyme-based counterparts.[8] Considering the growing importance of α-AAs in the *de novo* design of peptides, peptidomimetics and pharmaceuticals,[9] the cost-per-structure issue is a key factor in the quality assessment of a new synthetic method. Particularly, a high degree of stereocontrol accessible under operationally convenient conditions, such as an easily maintainable temperature and the use of air- and moisture-stable reagents,[10] is unarguably an essential requirement of a truly practical method. Taking all such aspects into account, one of the most economically sound chemical asymmetric syntheses of α-AAs is the one reported by Maruoka, who developed alkylations of achiral glycine Schiff bases **1** under phase-transfer catalysis (PTC) with chiral quaternary amines (Figure 1).[3b,11] Although



1 R^1 = alkyl, R^2 = H, Ph

2 X = alkyl, halogen

Figure 1. Achiral and chiral glycine equivalents of practical significance.

synthetically highly valuable, this process has still serious drawbacks related to the high cost of the chiral catalysts and the incomplete yields (~80%). Here, we report on an alternative protocol, featuring excellent stereochemical control achieved under PTC conditions at room temperature. The approach relies on the use of a specially designed and inexpensive glycine equivalent **2** possessing two elements of chirality: stereogenic centers and a chiral axis.[12]

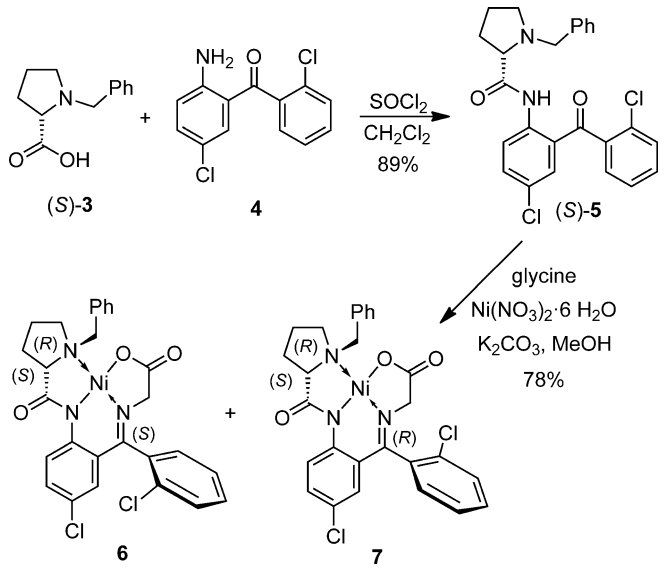
It is demonstrated that in the matched case of these stereocontrolling elements alkylations as well as aldol and Michael addition reactions can be conducted with virtually complete stereochemical control leading to excellent stereoselectivities [of commonly *dr*= >98:2]. Because Schiff bases **2** are hydrolytically stable under PTC conditions, high chemical yields can be achieved. Drawing inspiration from the many applications of glycine Schiff base Ni(II) complexes[13,14] for general asymmetric α-AA synthesis,[15] we designed proline-derived amide (*S*)-**5** as a new type of potential nickel chelator (Scheme 1). The synthesis of (*S*)-**5** involved a simple condensation of commercially available (*S*)-*N*-benzylproline [(*S*)-**3**] and 2-amino-2′,5-dichlorobenzophenone (**4**), which led to (*S*)-**5** in 89% yield.[16]

The central feature of (*S*)-**5** is that upon formation of the Schiff base with glycine and subsequent *in situ* complexation of the resulting imine with an Ni(II) salt, a metal complex is generated that bears two new elements of chirality. First, a stereogenic center at the prolinyl nitrogen and, second, a chiral axis between the imine carbon and the *ortho*-chlorophenyl group resulting from hindered rotation around the respective C–C bond. Whereas the new stereogenic center is cleanly induced with *R* configuration in high diastereoselectivity, the generation of the chiral axis is less determined (at the required elevated temperature of the metal complexation in methanol) resulting in the formation of two diastereomeric complexes **6** and **7**, which are formed in about a 1:2 ratio in high overall yield. Column chromatography allows separation of both complexes providing **6** and **7** in diastereomerically pure form. Their relative configurations were unambiguously determined by X-ray crystal structure analyses.[17] Accordingly, **6** and **7** have *S* and *R* configurations, respectively, at the chiral axes.

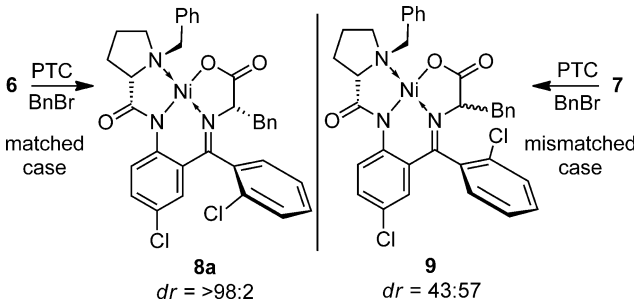
PTC benzylations were chosen as model reactions in order to determine the inductive potential of **6** and **7** in diastereoselective alkylations. The standard conditions involved the addition of tetrabutylammonium iodide (TBAI, 10 mol%), NaOH (30% aqueous), and 1,2-dichloroethane.[18] As shown in Scheme 2, the diastereoselectivities in the benzylation reactions of **6** and **7** differed significantly. Whereas the former led to a single product (**8a**) in high chemical yield, the latter afforded a diastereomeric mixture of the two corresponding benzylated products (**9**) in a 43:57 ratio.

Thus, in complex **6** the stereogenic elements cooperated (matched case), whereas in **7** this beneficial effect was missing (mismatched case). Consequently, complex **6** was considered valuable for the subsequent alkylation studies.

The optimization of the PTC conditions revealed that the alkylation reactions of **6** could be carried out under solid-liquid phase-transfer conditions, allowing avoidance of water as additional reaction medium. In terms of the substrate scope we were pleased to find that most products were formed with excellent diastereoselectivities (>98:2) in good yields after short reaction times (Table 1). All reactions of **6** with symmetrically substituted benzyl bromides gave the corresponding alkylation products (**8a–h**) in good yields with virtually complete stereoselectivity, regardless of the electronic nature of the substituents (Table 1, entries 1–8). *ortho*- and *meta*-substituted benzyl bromides reacted with the same efficiency in both yield and diastereoselectivity (Table 1, entries 9–13). Use of unsaturated alkyl bromides such as allyl and proparg-

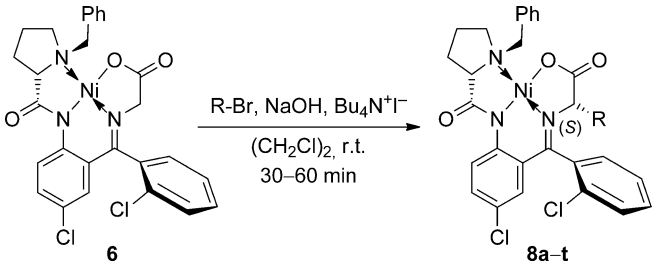


Scheme 1. Synthesis of Ni(II) complexes **6** and **7** containing elements of central and axial chirality.



Scheme 2. Benzylations of Ni(II) complexes **6** and **7** under PTC conditions.

Table 1. Alkylations of Ni(II) complex **6** under PTC conditions.[a]



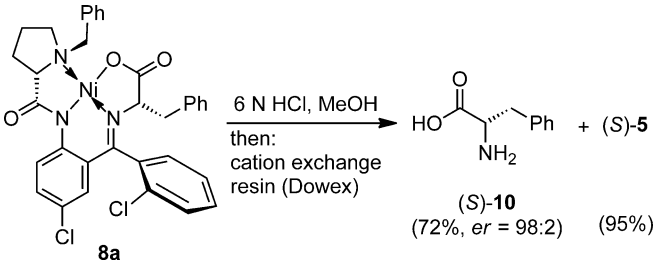
Entry	R	*dr*[b]	Yield[c] [%]
1	$C_6H_5CH_2$	>98:2	73 (**8a**)
2	4-F_3C-$C_6H_4CH_2$	>98:2	80 (**8b**)
3	4-Br-$C_6H_4CH_2$	>98:2	77 (**8c**)
4	4-NO_2-$C_6H_4CH_2$	>98:2	81 (**8d**)
5	4-$BrCH_2C_6H_4CH_2$	>98:2	73 (**8e**)
6	3,5-F_2-$C_6H_3CH_2$	>98:2	89 (**8f**)
7	3,5-$(MeO)_2$-$C_6H_3CH_2$	>98:2	88 (**8g**)
8	2,3,4,5,6-$F_5C_6CH_2$	>98:2	84 (**8h**)
9	2-Br-$C_6H_4CH_2$	>98:2	83 (**8i**)
10	2-I-$C_6H_4CH_2$	97:3	91 (**8j**)
11	3-F-$C_6H_4CH_2$	>98:2	90 (**8k**)
12	3-MeO-$C_6H_4CH_2$	>98:2	83 (**8l**)
13	3-NO_2-$C_6H_4CH_2$	>97:3	89 (**8m**)
14	CH_2=CH−CH_2	>98:2	76 (**8n**)
15	PhCH=CH−CH_2	>97:3	88 (**8o**)
16	HC≡C−CH_2	>98:2	89 (**8p**)
17	CH_3CH_2C≡C−CH_2	>98:2	81 (**8q**)
18	MeO_2CCH_2	>98:2	96 (**8r**)
19	2-naphthyl−CH_2	>98:2	87 (**8s**)
20[d]	Me	94:6	90 (**8t**)

[a] Use of **6** (0.07 mmol), alkyl bromide (0.17 mmol), NaOH (2.7 mmol) and $(n\text{-Bu})_4NI$ (0.007 mmol) in 1,2-dichloroethane (0.7 mL) at room temperature.
[b] Determined by ^1H NMR spectroscopy.
[c] After column chromatography.
[d] Use of methyl iodide as alkylating agent.

yl bromides also worked well leading to products **8n–q** in yields reaching 89% and excellent stereoselectivities (Table 1, entries 14–17). Particularly noteworthy is the alkylation of **6** with methyl bromoacetate, which led to aspartic acid derivative **8r** with a *dr* of >98:2 in almost quantitative yield (Table 1, entry 18). Finally, reactions of **6** with 2-(bromomethyl)naphthalene and methyl iodide afforded the corresponding products **8s** and **8t** as single diastereomers in 87% yield and as 94:6 diastereomeric mixtures in 90% yield, respectively (Table 1, entries 19 and 20).

The *S*-configuration of the newly created stereogenic center was established by X-ray crystal structure analysis of propargylinated complex **8p**.[17]

Increasing the scale of the reaction and applying 1 g of **6** in the alkylation with benzyl bromide afforded **8a** with the same excellent diastereoselectivity as on the smaller scale (>98:2, *cf.* Table 1, entry 1), and,



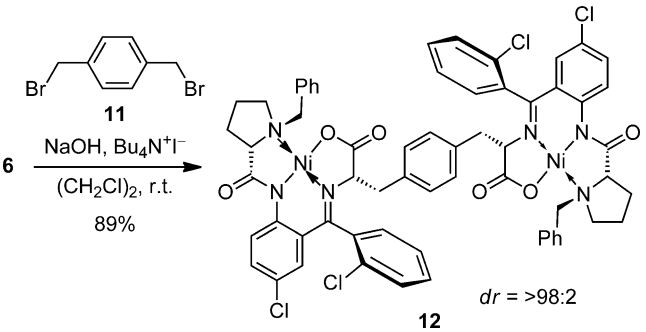
Scheme 3. Disassembly of **8a** to give (*S*)-phenylalanine [(*S*)-**10**].

to our delight, the yield significantly improved from 73% to 96%. By treatment of **8a** with 6N HCl in methanol under standard conditions,[19] the complex could be degraded leading to (*S*)-phenylalanine [(*S*)-**10**] with an *er* of 98:2 in 72% yield after purification by cation exchange resin (Dowex). Chiral amide (*S*)-**5** was recovered in 95% yield (Scheme 3).

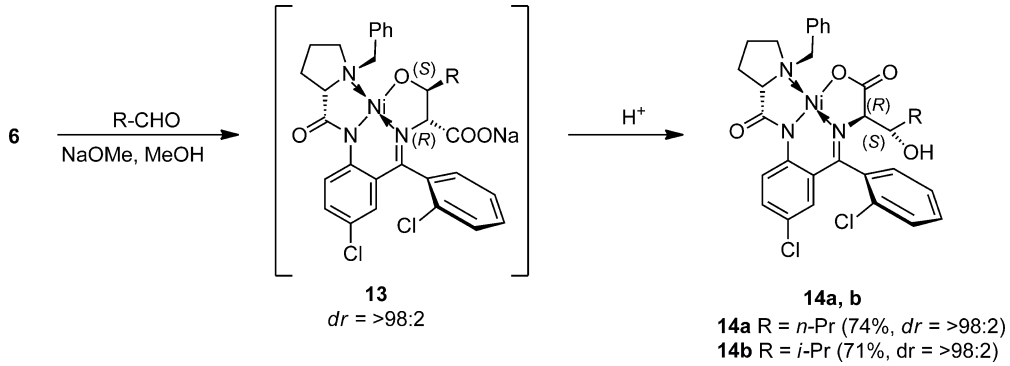
Considering the importance of bis-amino acids,[20] the alkylation of **6** with α,α′-dibromo-*para*-xylene (**11**) was studied (Scheme 4). Both electrophilic sites of **11** reacted well furnishing aryl-bridged dinickel complex **12** as a single product with a *dr* of >98:2 in 89% yield.

Aldol addition reactions of chiral glycine equivalents open a reliable and straightforward access to biologically important α-amino-β-hydroxy acids.[21] To illustrate the directing power of the newly developed system in such reactions, nickel complex **6** was treated with NaOMe in methanol and reacted under homogeneous conditions with *n*-butyraldehyde and 2-methylpropanal. As a result, the corresponding products **14a** and **14b** were obtained in 74% and 71% yields, respectively (Scheme 5). Under thermodynamic control, the stereoselectivity was complete leading to a single one out of the four theoretically possible diastereomers in both cases.[22]

The relative stereochemistry of product **14a** was determined by X-ray crystal structure analysis,[17] which revealed that the newly formed stereogenic centers



Scheme 4. Alkylation of **6** with α,α′-dibromo-*para*-xylene (**11**).



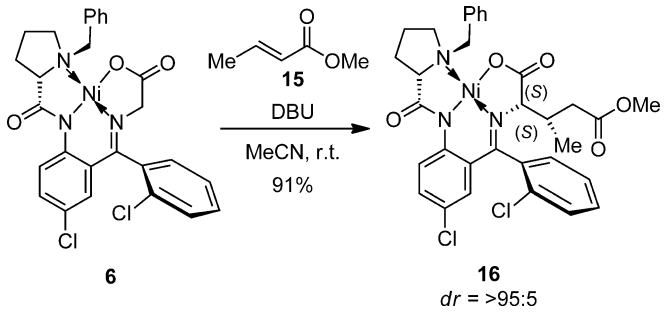
Scheme 5. Aldol additions of Ni(II) complex **6**.

had *R* and *S* configurations (as indicated in Scheme 5). This result suggests the intermediacy of a complex of type **13**,[23] in which the alkoxy moiety is bound to the central nickel ion. As a consequence, the sodium carboxylate group points down, away from the stereochemistry-controlling chloro substituent of the arene, and the R substituent at the alkoxy-bearing carbon is in the sterically favourable *trans*-position to the COONa group. Upon protonation, complex **13** rearranges to the final product **14**. As a result, the stereochemical preference in the aldol process is the same as that in the alkylation of complex **6** although the absolute configuration at the newly formed stereogenic center is opposite.

Michael additions are other important homologation reactions of glycine equivalents.[24] They give rise to a variety of structurally complex amino acids, such as β-substituted, χ-constrained derivatives with relevance for the design of *de novo* peptides.[25] In our study, we chose the addition of **6** to crotonic acid methyl ester (**15**) as a test reaction, as it is known to be a difficult transformation due to the formation of two consecutive stereogenic centers and the minimal steric impact of the methyl group.[26] To our delight, the Michael addition proceeded smoothly in acetonitrile with DBU as base (Scheme 6), and as in the other processes, the reaction was clean occurring at a high rate. The stereocontrol was complete, and only a single diastereomer was observed (91% yield). Using chiroptical properties and spectral data,[2,27] both new stereogenic centers were determined to have *S* configurations.

Having proven that nickel complex **6** was highly effective in controlling the stereochemistry in alkylation, aldol and Michael addition reactions, we wondered about a possible use of its diastereomer **7**, which was formed in significant quantities during the complex formation (Scheme 1). To this end we finally could demonstrate that under microwave irradiation a clean epimerization (by rotation around the chiral axis) occurred allowing us to convert pure diastereomer **7** into a 55:45 mixture of **6** and **7**. Chromatographic separation of the two diastereomers increased the overall yield of **6**, which proved beneficial for the aforementioned applications in asymmetric C–C bond formations.

In summary, we have developed a new chiral glycine equivalent having a combination of stereogenic centers and chiral axis and proved its applicability in a variety of representative alkylations with alkyl halides, as well as in aldol and Michael addition reactions. Of particular significance is the exceptional combination of virtually complete stereochemical control with operationally convenient room temperature conditions. Further applications of this synthetically interesting reagent are currently on-going in our laboratories.



Scheme 6. Representative Michael addition of Ni(II) complex **6**.

Experimental Section

Experimental procedures, full characterization of new products, copies of NMR spectra, *er* determinations and X-ray crystal data for **6**, **7**, **8p** and **14a** (CIF) can be found in the Supporting Information.

General Procedure for the Alkylation of Nickel Complexes 6 and 7

In a Schlenk flask equipped with a magnetic stirrer bar the Ni(II) complex (37.8 mg, 0.07 mmol), TBAI (2.5 mg,

0.007 mmol, 0.1 equiv.) and crushed NaOH (106.7 mg, 2.7 mmol, 40 equiv.) were dissolved in 1,2-dichloroethane (0.7 mL) under an argon atmosphere. The alkylation reagent (0.17 mmol, 2.5 equiv.) was added to the reaction mixture (liquid alkyl halides were dissolved in a small amount of 1,2-dichloroethane). The reaction was followed by TLC (DCM:acetone 4:1) until completion (30–60 min). The reaction mixture was washed with AcOH (5% aqueous solution, 5 mL) and the separated aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL each). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The product was purified by column chromatography (DCM:acetone 4:1 or 7:1).

Acknowledgements

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Asymmetric Synthesis of α-Amino Acids under Operationally Convenient Conditions

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