Asymmetric Synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-α,β-Dialkyl-α-amino Acids via Alkylation of Chiral Nickel(II) Complexes of Aliphatic α-Amino Acids with Racemic α-Alkylbenzyl Bromides

Vadim A. Soloshonok,* Thomas U. Boettiger, Shawna B. Bolene

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, USA
Fax +1(405)3256111; E-mail: vadim@ou.edu

Received 30 March 2008; revised 28 April 2008

Abstract: This study has demonstrated that the stereochemical outcome of the direct alkylation of nickel(II) complexes derived from chiral Schiff bases of glycine, alanine, 2-aminobutyric acid, and leucine with racemic α-methylbenzyl bromide depends on the steric bulk of the corresponding amino acid residue. In particular, the alkylation of the alanine complex was found to proceed with a synthetically useful level (90% de) of stereoselectivity offering a concise synthesis of enantiomerically pure (2*S*,3*S*)- or (2*R*,3*R*)-α,β-dimethylphenylalanines.

Key words: sterically constrained amino acids, alkylation, asymmetric synthesis, kinetic resolution

In the post-genomic era, the medicine-related sciences are currently exploring unprecedented opportunities in developing new approaches for detecting and treating human health disorders and diseases. It is expected that the information provided by the human genome sequence will revolutionize various multidisciplinary research fields, in particular, the rational design and synthesis of proteins, peptides, and tailor-made amino acids.[1–5] It is well established that incorporation of tailor-made amino acids, in particular sterically constrained derivatives, in a peptide can allow for efficient alteration of the peptide's native secondary and/or tertiary structure by inducing specific conformations.[5–8] In this regard, α,β-dialkyl substituted α-amino acids represent the least studied yet potentially most powerful and important class of such tailor-made sterically constrained amino acids.[8–10] It has been demonstrated that rational manipulation of the steric properties of the α- and β-alkyl groups in such amino acids might allow for a rational simultaneous control of the peptide backbone dihedral angles ϕ (phi), ψ (psi), and ω (omega), and most importantly, the torsional angles (chi) χ^1, χ^2, etc., determining the position of side-chain functional groups (Figure 1).[5–7] Taking into account that all these dihedral and torsional angles are of paramount importance in determining the conformation of peptides, incorporation of these sterically constrained amino acids into peptides might allow for a rational design of peptides with a presupposed three-dimensional structure.[5–7,11]

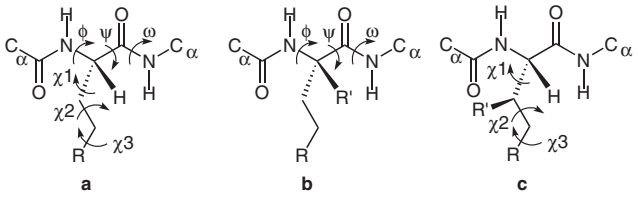
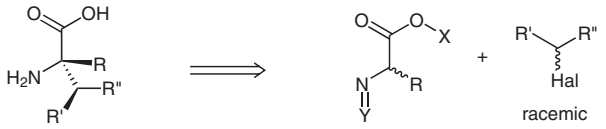


Figure 1 (a) Depiction of ϕ, ψ, ω, and χ dihedral angles for amino acid residues in peptides; (b) Restriction of ϕ, ψ, ω, angles by α-substitution; (c) restriction of χ angles by β-substitution



Scheme 1 Alkylation of chiral derivatives of α-amino acids with racemic *sec*-alkyl halides

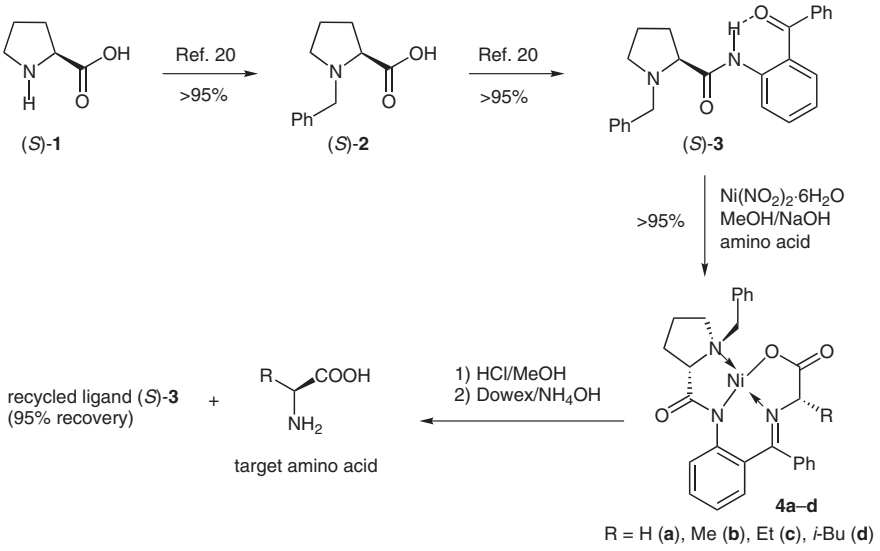
Analysis of the relevant literature[5,6,9–11] revealed that synthesis of the enantiomerically pure α,β-dialkyl substituted α-amino acids is virtually undeveloped. It is interesting to note that structurally less complicated either α- or β-monoalkyl substituted α-amino acids are readily available by the recently developed quite synthetically efficient catalytic and stoichiometric asymmetric approaches, most notably represented by the work of Shibasaki,[12] Maruoka and Ooi,[13] and Ohfune.[14] In contrast, only a single method reported by Davis allows for the preparation of α,β-dialkyl substituted α-amino acids in optically pure form via a tedious multistep procedure starting from enantiomerically pure 2*H*-azirine-2-carboxylate esters.[15]

As one can envision, methodologically more straightforward and concise approach to the target α,β-dialkyl substituted α-amino acids might be realized via direct alkylation of chiral derivatives of α-amino acids with racemic *sec*-alkyl halides (Scheme 1).

Feasibility of this approach was demonstrated by Seebach and Hruby via alkylation of chiral glycine and alanine equivalents BMI (1-Bz-, 1-Boc-, 1-Z- or 1-formyl-2-*tert*-butyl-3-methyl-4-imidazolidinones) with racemic 1-(phenyl)ethyl bromide (*rac*-**5**). The reactions were conducted at low temperatures (–60 °C, –78 °C), and the corresponding alkylation products were obtained in moderate to good

SYNTHESIS 2008, No. 16, pp 2594–2602
Advanced online publication: 08.07.2008
DOI: 10.1055/s-2008-1067172; Art ID: M01808SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of Illinois. Copyrighted material.



Scheme 2

chemical yields (58–82%) and in respectable diastereomeric purity (80–85% de).[16] Taking into account the potential synthetic value of this approach allowing for straightforward preparation of enantiomerically pure α,β-dialkyl substituted α-amino acids, further investigation of the corresponding alkylation reactions between other chiral equivalents of amino acids and racemic *sec*-alkyl halides might be of great interest to develop a generalized and convenient synthesis of this virtually unknown and unstudied type of sterically constrained amino acids.

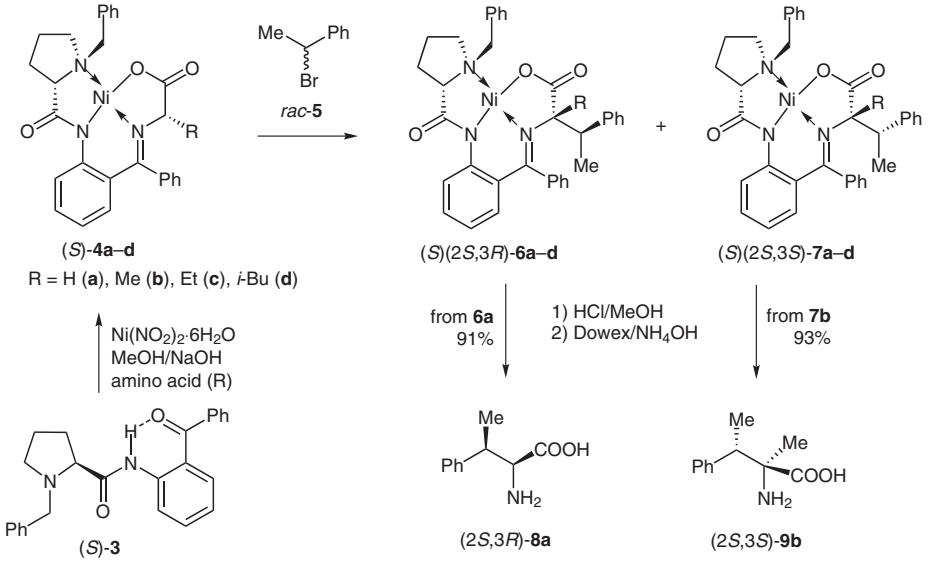
Here we report a full account[17] of our studies on the reactions between chiral Ni(II) complexes of glycine (*S*)-**4a**, alanine (*S*)(*S*,*R*)-**4b**, (*S*)(*S*,*R*)-α-aminobutyric acid **4c**, and (*S*)(*S*,*R*)-leucine **4d** (Scheme 2) with bromide *rac*-**5**, and provide a mechanistic rationale for the observed stereochemical outcome.

Among the numerous chiral equivalents of a nucleophilic glycine developed in the recent 25 plus years[10,18] for general asymmetric synthesis of α-amino acids, the *N*-benzylproline-derived Ni(II) complex **4a**, introduced by Belokon[19] represents one of the most successful designs. Seemingly low atom economy of complex **4a**, as a protected glycine derivative, is profoundly misleading as the chiral ligand **3** can be quantitatively recovered and reused, rendering the whole process as synthetically, practically, and economically efficient as any catalytic process in terms of chiral auxiliary consumption and cost of the final products. Recently we reported a convenient procedure for the large-scale synthesis of *N*-benzylproline **2**, its transformation to ligand **3**, and preparation of the glycine complex **4a**.[20] Practical asymmetric syntheses of various α-amino acids using the glycine equivalent **4a** is well documented by Belokon,[21,22] our,[22,23] and other[24] groups. An apparent synthetic advantage of complex **4a** over other chiral glycine equivalents is that it can be efficiently (>90% de, >90 yield) homologated via alkyl halide alkylation, aldol and Michael addition reactions under operationally convenient conditions, that is, without recourse to inert atmosphere, rigorously dried and degassed solvents, air- or moisture-sensitive reagents and low temperatures. Another advantage of this design is that, in principle, any other amino acid can be used instead of glycine for preparing the corresponding complexes of higher amino acids under the standard reaction conditions. Thus complexes derived from glycine **4a**, alanine **4b**, α-aminobutyric acid **4c**, and leucine **4d** (Scheme 2) were prepared in high chemical yields simply by heating a methanolic solution of ligand **3** and the corresponding amino acid in the presence of $Ni(NO_2)_2·6H_2O$ and NaOH. The alanine complex **4b** was isolated and used for the alkylation as a mixture of (*S*)(2*S*)- and (*S*)(2*R*)-diastereomers, while the complexes **4c**,**d**, containing bulkier substituents, were obtained in diastereomerically pure form.

Alkylation of Complexes 4a–d with *rac*-5

The alkylation reactions (Scheme 3) of complexes **4a**–**d** with *rac*-**5** were carried out under our standard conditions using a three-fold excess of *rac*-**5**, commercial grade DMF as a solvent, and powdered NaOH as a base. The reaction temperature was varied to study its influence on the stereochemical outcome. The results obtained are summarized in Table 1. The alkylation of the glycine complex **4a**, conducted at room temperature, occurred at a high rate giving rise to a mixture of two major diastereomeric products (*S*)(2*S*,3*R*)-**6a** and (*S*)(2*S*,3*S*)-**7a** in a ratio of 1.2:1 (entry 1). Besides the major diastereomers **6a** and **7a**, up to 20% of two α-*R* configured products were also detected in the crude reaction mixture. Lowering the reaction temperature expectedly decreased the rate of the alkylation (entries 2, 3 vs. 1), however, the diastereoselectivity was not markedly improved. Slow reaction rates brought about formation of some by-products (up to 10%) lowering the yield of the target products. We also tried the phase-transfer conditions for the alkylation of the glycine complex **4a**

Downloaded by: University of Illinois. Copyrighted material.



Scheme 3

with bromide *rac*-**5**. In this case (entry 4), the reaction conducted at room temperature proceeded at a substantially slower rate resulting, however, in a clean formation of diastereomers **6a** and **7a** in a ratio of 1.5:1, the same as the stereochemical outcome of the alkylation carried out at 0 °C under the homogeneous conditions (entry 4 vs. 2). Complexes **6a** and **7a** were easily isolated in diastereomerically pure form by column chromatography on silica gel. Complex **6a** was disassembled, under standard conditions, to afford enantiomerically pure (2*S*,3*R*)-β-methylphenylalanine (**8a**) (Scheme 3).

In sharp contrast to the reactions of the glycine complex **4a**, the alkylation of the alanine derivative **4b** with *rac*-**5**, conducted at room temperature, occurred with appreciable diastereoselectivity (entry 5). Moreover, the formation of the α-*R* configured products was substantially reduced (<5%) allowing direct isolation of the major product (*S*)(2*S*,3*S*)-**7b** in good (75%) chemical yield. Once again, in contrast to the alkylation of the glycine complex **4a**, lowering the reaction temperature lead to a noticeable increase in the diastereoselectivity (entries 6, 7 vs. 2, 3). Thus, the reaction conducted at –15 °C gave rise to the major diastereomer **7b** with synthetically useful (entry 7) stereoselectivity. Taking into account that in this reaction we used the racemic alkyl halide **5** for alkylation of the diastereomeric mixture of the alanine complex **4b**, the obtained stereochemical outcome of >90% de was truly remarkable. Decomposition of the complex **7b** afforded the enantiomerically pure α,β-dimethylphenylalanine (**9b**) (Scheme 3), which is not directly available by the literature methods.

With these encouraging results, we next studied the alkylations of complexes **4c**,**d**, assuming that bulkier ethyl and, in particular, isobutyl groups might allow for increased stereoselectivity. Surprisingly, the alkylation of the ethyl-containing **4c** with *rac*-**5** occurred at a noticeably slower rate giving rise to a mixture of (*S*)(2*S*,3*R*)-**6c** and (*S*)(2*S*,3*S*)-**7c** in a low ratio of 1:1.6 (entry 8). Attempts to improve the stereochemical outcome by lowering the reaction temperature were unsuccessful. Thus, the reaction conducted at 0 °C gave virtually the same ratio of the diastereomers as was observed in the room temperature reaction (entry 9 vs. 8), while the alkylation at –10 °C was too sluggish (entry 10) to isolate the products in

Table 1 Reactions of Complexes **4a–d** with *rac*-**5**[a]

Entry	**4a–d**	Temp (°C)	Time (min)	Yield (%)[b]	Ratio of **6**/**7**[c]
1	**a**	25	10	95	1.2:1
2	**a**	0	25	84	1.5:1
3	**a**	–15	75	89	1.9:1
4	**a**	25[d]	240	96	1.5:1
5	**b**	25	70	96	1:4.0
6	**b**	0	110	90	1:6.5
7	**b**	–15	180	94	1:20.0
8	**c**	25	90	87	1:1.6
9	**c**	0	210	87	1:1.7
10	**c**	–10	540	–	–
11	**d**	25	180	81	1:1.7
12	**d**	0	480	–	–

[a] All reactions were run in commercial grade DMF under N_2.
[b] Combined yield of all diastereomeric products.
[c] Ratio of diastereomeric products (*S*)(2*S*,3*R*)-**6**/(*S*)(2*S*,3*S*)-**7** was determined on the crude reaction mixtures by ^{1}H NMR spectra (500 MHz). In particular, characteristic and well-separated signals of aromatic protons in the region 8.00–8.25 ppm were used for the determination.
[d] The reaction was conducted under phase-transfer conditions.

Downloaded by: University of Illinois. Copyrighted material.

amount suitable for reliable determination of the stereochemical outcome. Even slower reaction rates and lower stereoselectivity were observed in the alkylation of the leucine-derived complex **4d** (entries 11, 12), indicating that an increase in the steric bulk of the amino acid residue interferes with the reactivity of the Ni(II) complexes and stereoselectivity of the alkylation.

Assignment of the Absolute Configuration

The absolute configuration of products **6a–d**, **7a–d**, and **8**, **9** was assigned using chiroptical properties of the products, ^{1}H NMR patterns, and correlations with literature data. The absolute configuration of the α-stereogenic carbon of the corresponding amino acid residues in all Ni(II) complexes can be easily assigned on the basis of their optical rotation. As it has been established in numerous studies of the Ni(II) complexes of this type derived form various amino acids,[25] the complexes containing α-*S* configured amino acids have a positive sign of optical rotation with magnitude ranging from +1500 to +3000, while the complexes containing amino acids of α-*R* absolute configuration show the negative sign of –1000 to –2000. Thus products **6a** and **7a**, obtained in the alkylation of the glycine complex **4a**, showed optical rotations of +1980 and +2350, suggesting that both contained residues of β-methylphenylalanine of α-*S* absolute configuration. The relative configuration of the amino acid residue in **6a** and **7a** was assigned based on their ^{1}H NMR spectra. Thus, in **6a** the α-proton at 4.12 ppm appears as a doublet with $J_{\alpha H,\beta H}$ = 3.0 Hz, while in the ^{1}H NMR spectrum of **7a** the α-proton at 4.06 ppm is a doublet with $J_{\alpha H,\beta H}$ = 6.0 Hz. A comparison of these chemical shifts and coupling constants with the literature data[26] reported for the diastereomeric Ni(II)-complexes containing (2*S*,3*R*)- and (2*S*,3*S*)-3-phenylglutamic acids reveals very close similarity, suggesting that product **6a** has 2*S*,3*R* and **7a** 2*S*,3*S* absolute configuration. These assignments are also in perfect accord with the optical and physicochemical properties recorded for the free amino acids **8** obtained from complex **6a**, which showed sign and magnitude of optical rotation as well as ^{1}H NMR pattern matching the literature data reported for the (2*S*,3*R*)-β-methylphenylalanine.[27]

The absolute configuration of the complexes **6b** and **7b**, containing residue of the α,β-(dimethyl)phenylalanine was assigned as α-*S* on the basis of their positive optical rotations (+2254 and +2095, respectively). The configuration of the β-stereogenic carbon of the amino acid residue was determined by comparison of the chiroptical and ^{1}H NMR data recorded for free amino acid **9**, obtained from complex **7b**, with those reported in the literature for (2*S*,3*S*)-α,β-dimethylphenylalanine.[15b] Finally, the absolute configuration of the amino residues in complexes **6c**,**d** and **7c**,**d** was determined based on their chiroptical properties as well as pattern of ^{1}H NMR spectra. Since products **6c**,**d** and **7c**,**d** showed positive optical rotation, the absolute configuration of the α-stereogenic carbon of the corresponding amino acids in **6c**,**d** and **7c**,**d** was assigned as 2*S*. Absolute configuration of the β-stereogenic centers of the amino acids in **6c**,**d** and **7c**,**d** was made considering clear similarity of their ^{1}H NMR spectra with those registered for **6a**,**b** and **7a**,**b**. Thus, in all ^{1}H NMR spectra of 2*S*,3*R*-configured products **6a**,**b** the doublet of the β-methyl appears at the expected 1.15–1.20 ppm, while in the spectra of products **7a–d** of 2*S*,3*S* absolute configuration, the doublet of the β-methyl group is shifted downfield to the region of 2.00–2.20 ppm. As shown in the previous work,[21–23] such downfield shift is characteristic for the alkyl groups situated directly under the Ni(II) atom. On the other hand, in the ^{1}H NMR spectra of 2*S*,3*R*-diastereomers **6a–d**, in which the phenyl of the side chain is located under the Ni(II) atom, one of the γ-protons of the proline ring is shifted about 0.5–0.6 ppm upfield, due to the effect of the diamagnetic ring current of the phenyl.[26]

Rationale for the Stereochemical Outcome

Explanation of the observed stereochemical outcome in the alkylation reactions under study, can be divided into three separate major questions: 1) in the reaction of the glycine complex **4a** with *rac*-**5**, why is the (*S*)(2*S*,3*R*)-configured diastereomer **6a** preferred over the (*S*)(2*S*,3*S*)-**7a** one; 2) why does the alkylation of the alanine complex **4b** show overwhelming preference for the opposite (*S*)(2*S*,3*S*)-stereochemistry giving rise to the diastereomer **7b** in synthetically useful chemical yield; and 3) why does the further increase in the steric bulk of the amino acid side chain, the reactions of the complexes **4c**,**d** with *rac*-**5**, result in an unexpected decrease in diastereoselectivity? As an approach to the mechanistic rationale for the stereochemical preferences observed, we constructed all six theoretically possible transition states (TSs), representing the interactions between the *si*-face of the corresponding enolate and the *S*- and *R*-enantiomers of the bromide **5** (Figure 2). Based on the substantial experimental data and mechanistic rationale for the stereochemical preferences we previously obtained in the Michael addition reactions of complex **4a** and its analogues with (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones,[28] we can rule out the possibility of TSs **B** and **D** formation, since the phenyl group cannot be sterically accommodated directly under the nickel. Formation of the TSs **C** and **E**, in which the phenyl group points toward the ketimine phenyl, also seems to be unlikely due to the apparent steric repulsive interactions between these two phenyl groups. Therefore, we can assume that TSs **A** and **F**, which allows for minimization of all steric interactions, might be the most plausible candidates. Considering the steric interaction of the methyl group in the reaction of the glycine complex **4a** (R = H), we can conclude that TS **F** should be more thermodynamically favorable than TS **A**. Thus, in TS **F** the methyl interacts with the enolate hydrogen and nitrogen, while in TS **A** the methyl is located between the enolate oxygen and nitrogen. Accordingly, the observed prefer-

Downloaded by: University of Illinois. Copyrighted material.

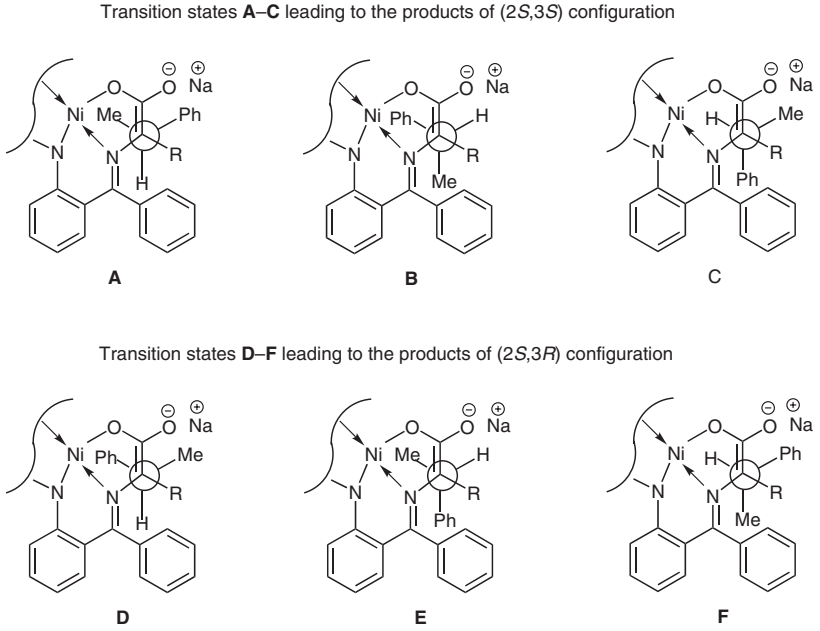


Figure 2 Transition states **A**–**F** in the reactions between complexes **4a**–**d** and *rac*-**5**

ence of about 2:1 of the 2*S*,3*R*-diastereomer can be reasonably accounted for on the basis of steric interactions in TSs **A** and **F**. When the R group is Me, the reactions of the alanine complex **4b** with bromide **5**, the mode of the stereochemical preferences in TSs **A** and **F** is reversed. Thus, in the enolate derived from the glycine complex the hydrogen is the smallest substituent, while for alanine the methyl is the largest group of the corresponding enolate moiety. Considering the TSs **A** and **F**, we can expect that the TS **F** might be significantly disfavored relative to TS **A**, thus accounting for the observed high 2*S*,3*S*-diastereoselectivity. Finally, we can suggest that an increase in the steric bulk of the substituent R might interfere with the formation of both TSs **A** and **F**. Thus, substitution of the methyl (alanine complex **4b**) for ethyl (**4c**) or isobutyl (**4d**) might lead to increased repulsive steric interactions with the Ni(II) complex ketimine phenyl, as well as with the phenyl group of the incoming electrophile, disfavoring the formation of both TSs **A** and **F**. This detrimental effect of the substituents bulkier than methyl on the formation of the TS seems quite plausible to account for the low reactivity and diastereoselectivity observed in the reactions of complexes **4c**,**d** with bromide *rac*-**5**.

In summary, this study has demonstrated that the stereochemical outcome of the direct alkylation of Ni(II) complexes derived from chiral Schiff bases of glycine **4a**, alanine **4b**, 2-aminobutyric acid **4c** and leucine **4d** with racemic α-methylbenzyl bromide (**5**) dramatically depended on the steric bulk of the amino acid residue. In particular the reaction of the alanine complex **4b**, was found to proceed with a high level (90% de) of stereoselectivity offering a methodologically advantageous approach for preparing enantiomerically pure (2*S*,3*S*)- or (2*R*,3*R*)-α,β-dimethylphenylalanine, depending on the (*S*)- or (*R*)-proline containing starting Ni(II) complex **4b**.

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under atmosphere without any special caution to exclude air. Optical rotations, ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ solutions at 299.95 and 75.42 MHz, respectively, on instruments available in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS as the internal standard. Yields refer to isolated yields of products greater than 95% purity as estimated by ^{1}H, ^{13}C NMR, and high-resolution mass spectrometry (HRMS-ESI).

Complexes **4a**,**b** were prepared according to the literature procedure.[20] For preparing new complexes **4c**,**d** the same procedure was followed except that *rac*-2-aminobutyric acid and (*S*)-leucine were used in the place of glycine or alanine.

Ni(II) Complex 4c of the Schiff Base of (*S*)-BPB {[(*S*)-*o*-[*N*-(*N*-Benzylprolyl)amino]benzophenone} with (*S*)-2-Aminobutyric Acid

R_f = 0.25 (acetone–hexanes, 1:1); mp 290–291 °C; $[\alpha]_D^{25}$ +2565 (*c* 0.144, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.36 (3 H, t, *J* = 6.9 Hz), 1.50–2.23 (5 H, m), 2.48–2.60 (1 H, m), 2.69–2.85 (1 H, m), 3.42–3.58 (2 H, m), 3.60, 4.45 (2 H, AB, *J* = 12 Hz), 3.85–3.93 (1 H, m), 6.60–7.55 (11 H, m), 8.04 (2 H, d, *J* = 7.2 Hz), 8.15 (1 H, d, *J* = 7.5 Hz).

HRMS: *m*/*z* calcd for $C_{29}H_{29}N_3NiO_3$ [M + H]$^+$: 526.1614; found: 526.1652.

Ni(II) Complex 4d of the Schiff Base of (*S*)-BPB with (*S*)-Leucine

R_f = 0.35 (acetone–hexanes, 1:1); mp 254–257 °C; $[\alpha]_D^{25}$ +2448 (*c* 0.175, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.33 (3 H, d, *J* = 6.6 Hz), 0.86 (3 H, d, *J* = 6.6 Hz), 1.29–1.41 (1 H, m), 1.85–2.28 (3 H, m), 2.42–2.62 (2 H, m), 2.68–2.81 (1 H, m), 3.43–3.51 (2 H, m), 3.55, 4.45 (2 H, AB, *J* = 12.6 Hz), 3.61–3.80 (1 H, m), 3.88 (1 H, dd, *J* = 10.8, 7.2 Hz), 6.59–6.69 (2 H, m), 6.90–6.96 (1 H, m), 7.08–7.54 (8 H, m), 8.05 (3 H, d, *J* = 7.2 Hz).

HRMS: *m*/*z* calcd for $C_{31}H_{33}N_3NiO_3$ [M + Na]$^+$: 576.1773; found: 576.1757.

Downloaded by: University of Illinois. Copyrighted material.

Alkylation of Complexes 4a–d with *rac*-5; General Procedure

Powdered NaOH (100 mmol, 10 equiv) was added to a solution of Ni(II) complex **4a**–**d** (10 mmol, 1 equiv) in DMF (20 mL) under stirring. Then, the bromide *rac*-**5** (25 mmol, 3 equiv) dissolved in DMF (5 mL) was added to the solution. The mixture was stirred under N_2 and the reaction progress was monitored by TLC. Upon completion [complete consumption of the Ni(II) complex], the mixture was poured over ice, and the precipitated material was collected by filtration and dried in vacuo. A small amount of the crude mixture was used to determine the diastereomeric ratio of the products, the rest was subjected to column chromatography on silica gel using acetone–hexanes (1:1) as an eluent to isolate the diastereomerically pure products.

Ni(II) Complex (*S*)(2*S*,3*R*)-6a of the Schiff Base of (*S*)-BPB with (2*S*,3*R*)-3-Methylphenylalanine

R_f = 0.36 (acetone–hexanes, 1:1); mp 253–258 °C; $[\alpha]_D^{25}$ +1980 (*c* 0.15, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.145 (3 H, d, *J* = 7.5 Hz), 1.35–1.49 (1 H, m), 1.71–1.87 (1 H, m), 1.89–1.98 (1 H, m), 2.17–2.27 (2 H, m), 2.74–2.91 (2 H, m), 3.25 (1 H, t, *J* = 8.7 Hz), 3.40, 4.24 (2 H, AB, *J* = 12.8 Hz), 4.12 (1 H, d, *J* = 3.3 Hz), 6.63–6.74 (2 H, m), 7.01–7.05 (1 H, m), 7.09–7.17 (2 H, m), 7.23–7.34 (3 H, m), 7.36–7.58 (8 H, m), 7.97 (2 H, d, *J* = 6.9 Hz), 8.27 (1 H, d, *J* = 8.7 Hz).

HRMS: *m*/*z* calcd for $C_{35}H_{33}N_3NiO_3$ [M + H]$^+$: 602.1954; found: 602.1956.

Ni(II) Complex (*S*)(2*S*,3*S*)-7a of the Schiff Base of (*S*)-BPB with (2*S*,3*S*)-3-Methylphenylalanine

R_f = 0.31 (acetone–hexanes, 1:1); mp 213–216 °C; $[\alpha]_D^{25}$ +2350 (*c* 0.15, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 2.00 (3 H, d, *J* = 7.2 Hz), 2.05–2.23 (2 H, m), 2.53–2.69 (1 H, m), 2.87–2.98 (1 H, m), 3.46–3.58 (3 H, m), 3.58, 4.45 (2 H, AB, *J* = 12.8 Hz), 3.73–3.84 (1 H, m), 4.06 (1 H, d, *J* = 6.0 Hz), 6.20 (1 H, d, *J* = 7.8 Hz), 6.51–6.56 (1 H, m), 6.58–6.65 (1 H, m), 6.66–6.73 (2 H, m), 7.04–7.33 (9 H, m), 7.42–7.49 (2 H, m), 8.04 (2 H, d, *J* = 7.2 Hz), 8.22 (1 H, d, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 16.3, 23.4, 30.8, 45.4, 56.7, 63.1, 70.5, 76.2, 120.5, 123.0, 126.3, 126.8, 127.5, 127.8, 128.2, 128.3, 128.7, 128.8, 129.4, 131.4, 132.2, 133.1, 133.5, 133.6, 140.9, 142.1, 170.6, 176.9, 180.1.

HRMS: *m*/*z* calcd for $C_{35}H_{33}N_3NiO_3$ [M + H]$^+$: 602.1954; found: 602.1951.

Besides the major products **6a** and **7a**, the α-*R* configured diastereomer was isolated in up to 20% yield. The (*S*)(2*R*,3*S*) absolute configuration was determined by its conversion to the corresponding (*S*)(2*S*,3*S*)-**7a** by the α-epimerization under the action of NaOH in DMF.

Ni(II) Complex of the Schiff Base of (*S*)-BPB with (2*R*,3*S*)-3-Methylphenylalanine

R_f = 0.44 (acetone–hexanes, 1:1); mp 207–213 °C; $[\alpha]_D^{25}$ –1996 (*c* 0.122, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.82–0.98 (1 H, m), 1.18 (3 H, d, *J* = 7.2 Hz), 1.25–1.42 (1 H, m), 1.78–1.88 (1 H, m), 1.98–2.15 (1 H, m), 2.42–2.53 (1 H, m), 2.96 (1 H, dq, *J* = 7.2, 3.6 Hz), 3.32, 3.45 (2 H, AB, *J* = 14.2 Hz), 3.34 (1 H, dd, *J* = 9.3, 3.2 Hz), 3.78 (1 H, ddd, *J* = 11.4, 7.5, 3.8 Hz), 4.11 (1 H, d, *J* = 3.6 Hz), 6.73–6.79 (1 H, m), 6.82–6.87 (1 H, dd, *J* = 8.3, 1.6 Hz), 7.09–7.19 (3 H, m), 7.25–7.36 (6 H, m), 7.44–7.51 (1 H, m), 7.52–7.99 (6 H, m), 8.46 (1 H, d, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 18.0, 24.1, 31.8, 45.9, 55.3, 59.5, 69.0, 76.3, 121.0, 123.8, 126.5, 127.5, 128.1, 128.2, 128.9, 129.0, 129.1, 129.5, 130.0, 130.3, 132.0, 132.1, 132.9, 134.0, 134.4, 141.4, 143.4, 171.0, 177.2, 182.0.

HRMS: *m*/*z* calcd for $C_{35}H_{33}N_3NiO_3$ [M + Na]$^+$: 624.1773; found: 624.1772.

Ni(II) Complex (*S*)(2*S*,3*R*)-6b of the Schiff Base of (*S*)-BPB with (2*S*,3*R*)-2,3-Dimethylphenylalanine

R_f = 0.43 (acetone–hexanes, 1:1); mp 121–123 °C; $[\alpha]_D^{25}$ +2254 (*c* 0.178, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 3 H), 1.43 (3 H, d, *J* = 7.0 Hz), 1.49–1.56 (1 H, m), 1.94–2.03 (2 H, m), 2.11–2.22 (2 H, m), 3.02–3.05 (1 H, m), 3.25 (1 H, dd, *J* = 7.9, 9.3 Hz), 3.48 (1 H, d, *J* = 12.6 Hz), 3.47–3.51 (1 H, m), 4.27 (1 H, d, *J* = 12.6 Hz), 6.54–6.60 (2 H, m), 7.03–7.05 (1 H, m), 7.07–7.09 (1 H, m), 7.10–7.16 (1 H, m), 7.27–7.51 (11 H, m), 8.01 (2 H, d, *J* = 7.1 Hz), 8.22 (1 H, d, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 16.3, 22.9, 28.0, 30.2, 48.8, 57.3, 63.8, 69.9, 81.3, 120.1, 122.9, 127.1, 127.3, 127.6, 127.7, 127.8, 128.6, 129.2, 129.6, 130.9, 131.5, 131.8, 133.4, 133.9, 137.3, 142.3, 142.5, 171.8, 179.7, 180.3.

HRMS (FAB): *m*/*z* calcd for $C_{36}H_{35}N_3O_3Ni$ [M + H]$^+$: 616.2110; found: 616.2106.

Ni(II) Complex (*S*)(2*S*,3*S*)-7b of the Schiff Base of (*S*)-BPB with (2*S*,3*S*)-2,3-Dimethylphenylalanine

R_f = 0.36 (acetone–hexanes, 1:1); mp 277–279 °C; $[\alpha]_D^{25}$ +2095 (*c* 0.125, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.67 (3 H, s), 1.66 (3 H, d, *J* = 6.7 Hz), 2.08–2.13 (1 H, m), 2.18–2.23 (1 H, m), 2.63–2.73 (1 H, m), 2.99–3.06 (1 H, m), 3.41–3.50 (1 H, m), 3.52–3.56 (3 H, m), 4.45 (1 H, d, *J* = 12.7 Hz), 4.85 (1 H, d, *J* = 7.7 Hz), 6.09–6.13 (1 H, m), 6.30–6.32 (1 H, m), 6.48–6.51 (1 H, m), 6.83–6.87 (1 H, m), 7.00–7.03 (1 H, m), 7.07–7.11 (2 H, m), 7.17–7.33 (9 H, m), 8.13 (2 H, d, *J* = 7.2 Hz), 8.21 (1H, d, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 16.7, 20.6, 23.1, 30.5, 52.8, 56.6, 63.0, 70.6, 81.9, 120.0, 122.2, 125.9, 126.8, 127.0, 127.1, 127.6, 128.0, 128.3, 128.4, 128.5, 129.2, 129.6, 131.0, 131.5, 133.1, 133.5, 135.7, 139.6, 141.4, 169.7, 178.5, 179.4.

HRMS (FAB): *m*/*z* calcd for $C_{36}H_{35}N_3O_3Ni$ [M + H]$^+$: 616.2110; found 616.2106.

Ni(II) Complex (*S*)(2*S*,3*R*)-(6c) of the Schiff Base of (*S*)-BPB with (2*S*,3*R*)-2-Ethyl-3-methylphenylalanine

R_f = 0.40 (acetone–hexanes, 1:1); mp 216–222 °C; $[\alpha]_D^{25}$ +1492 (*c* 0.204, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.98 (3 H, t, *J* = 7.2 Hz), 1.251 (3 H, d, *J* = 7.2 Hz), 1.41–1.55 (2 H, m), 1.66–1.81 (1 H, m), 1.85–1.95 (1 H, m), 1.97–2.23 (3 H, m), 2.87–2.97 (1 H, m), 3.21 (1 H, dd, *J* = 9.3, 7.7 Hz), 3.37, 4.11 (2 H, AB, *J* = 12.3 Hz), 3.48 (1 H, q, *J* = 7.2 Hz), 6.49–6.62 (2 H, m), 7.04–7.11 (1 H, m), 7.13–7.20 (1 H, m), 7.24–7.34 (4 H, m), 7.41–7.53 (8 H, m), 8.02 (1 H, d, *J* = 8.4 Hz), 8.13 (2 H, d, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 0.2, 9.8, 16.0, 22.9, 30.1, 30.4, 45.8, 57.9, 64.4, 70.7, 86.1, 120.1, 123.2, 127.0, 127.1, 127.6, 128.0, 128.1, 128.3, 128.4, 128.5, 129.2, 129.4, 131.2, 131.3, 133.4, 134.0, 137.0, 142.0, 143.2, 171.1, 179.1, 180.0.

HRMS: *m*/*z* calcd for $C_{37}H_{37}N_3NiO_3$ [M + H]$^+$: 630.2267; found 630.2256.

Ni(II) Complex (*S*)(2*S*,3*S*)-7c of the Schiff Base of (*S*)-BPB with (2*S*,3*S*)-2-Ethyl-3-methylphenylalanine

R_f = 0.37 (acetone–hexanes, 1:1); mp 257–260 °C; $[\alpha]_D^{25}$ +1719 (*c* 0.203, $CHCl_3$).

Downloaded by: University of Illinois. Copyrighted material.

^{1}H NMR ($CDCl_3$): δ = 0.83 (3 H, t, *J* = 7.2 Hz), 1.09–1.25 (1 H, m), 1.62–1.76 (1 H, m), 2.00–2.18 (2 H, m), 2.37 (3 H, d, *J* = 7.2 Hz), 2.47–2.64 (1 H, m), 2.67–2.79 (1 H, m), 3.22–3.38 (1 H, m), 3.40–3.50 (2 H, m), 3.63, 4.43 (2 H, AB, *J* = 12.6 Hz), 3.69–3.79 (1 H, m), 6.58–6.68 (4 H, m), 7.02–7.14 (5 H, m), 7.16–7.22 (1 H, m), 7.36 (2 H, t, *J* = 7.8 Hz), 7.41–7.49 (2 H, m), 7.52–7.60 (2 H, m), 7.93 (1 H, d, *J* = 8.4 Hz), 8.19 (2 H, d, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 0.4, 9.7, 18.2, 23.6, 31.0, 32.9, 45.5, 57.8, 64.7, 71.2, 85.7, 120.9, 124.2, 127.0, 127.3, 127.6, 128.2, 128.5, 128.9, 129.1, 129.4, 129.7, 129.9, 131.6, 131.7, 133.4, 134.4, 136.9, 140.5, 141.6, 172.4, 179.3, 180.6.

HRMS: *m*/*z* calcd for $C_{37}H_{37}N_3NiO_3$ [M + Na]$^+$: 652.2086; found: 652.2097.

Ni(II) Complex (*S*)(2*S*,3*R*)-6d of the Schiff Base of (*S*)-BPB with (2*S*,3*R*)-2-Isobutyl-3-methylphenylalanine

R_f = 0.56 (acetone–hexanes, 1:1); mp 268–272 °C; $[\alpha]_D^{25}$ +1602 (*c* 0.175, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 0.99 (3 H, d, *J* = 7.2 Hz), 1.23 (6 H, dd, *J* = 7.2, 4.2 Hz), 1.35–1.49 (1 H, m), 1.55–2.24 (7 H, br m), 2.77 (1 H, dt, *J* = 12.3, 6.6 Hz), 3.22 (1 H, t, *J* = 8.9 Hz), 3.38, 4.32 (2 H, AB, *J* = 12.6 Hz), 3.51 (1 H, q, *J* = 7.2 Hz), 6.54–6.64 (2 H, m), 7.08 (1 H, ddd, *J* = 8.4, 6.0, 2.5 Hz), 7.17–7.35 (5 H, m), 7.38–7.60 (8 H, m), 7.83 (1 H, d, *J* = 7.8 Hz), 8.06 (2 H, d, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 16.1, 21.0, 23.1, 24.1, 25.3, 30.7, 44.7, 45.6, 58.2, 64.2, 70.2, 83.5, 120.6, 124.1, 127.2, 127.5, 127.9, 128.6, 128.7, 128.8, 128.9, 129.2, 129.5, 129.8, 131.3, 131.7, 133.4, 137.2, 141.9, 143.5, 172.4, 180.2, 180.6.

HRMS: *m*/*z* calcd for $C_{39}H_{41}N_3NiO_3$ [M + H]$^+$: 658.2580; found: 658.2584.

Ni(II) Complex (*S*)(2*S*,3*S*)-7d of the Schiff Base of (*S*)-BPB with (2*S*,3*S*)-2-Isobutyl-3-methylphenylalanine

R_f = 0.44 (acetone–hexanes, 1:1); mp 131–135 °C.

^{1}H NMR ($CDCl_3$): δ = 0.73–3.88 (38 H, m), 4.12 (1 H, d, *J* = 12.9 Hz), 4.29 (0.4 H, d, *J* = 12.3 Hz), 4.58 (0.6 H, d, *J* = 12.3 Hz), 6.55–6.77 (7.4 H, m), 7.03–7.83 (35.4 H, m), 8.02 (0.4 H, d, *J* = 8.4 Hz), 8.15 (1 H, d, *J* = 6.9 Hz), 8.23 (0.6 H, d, *J* = 6.9 Hz).

HRMS: *m*/*z* calcd for $C_{39}H_{41}N_3NiO_3$ [M + H]$^+$: 658.2580; found: 658.2596.

Decomposition of Compounds 6a and 7b and Isolation of Free Amino Acids 8a and 9b; General Procedure[22m]

A solution of the complex **6a** or **7b** (22.5 mmol) in MeOH (90 mL) was slowly added to a mixture of aq 3 N HCl and MeOH (180 mL, 1:1) at 70 °C with stirring. When the red color of the Ni(II) complex had disappeared, the mixture was evaporated to dryness under vacuum. H_2O (120 mL) was added, and the resultant mixture was treated with an excess of NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated under vacuum to afford the free chiral ligand (93–98%). The aqueous phase was evaporated under vacuum and redissolved in a minimum amount of H_2O and loaded on a Dowex 50 × 2 100 ion-exchange column, which was washed with H_2O until neutral. The column was then washed with 8% aq NH_4OH. First fraction (350 mL) was collected and evaporated under vacuum to afford the corresponding amino acids **8a** (91%) or **9b** (93%), respectively.

(2*S*,3*R*)-3-Methylphenylalanine (8a)

Mp 193–194 °C; $[\alpha]_D^{25}$ –5.9 (*c* 1.0, H_2O) [Lit.[13a] –5.3 (*c* 0.75, H_2O)].

^{1}H NMR (H_2O, dioxane as internal standard at δ = 3.55): δ = 1.18 (3 H, d, *J* = 7.2 Hz), 3.33 (1 H, qd, *J* = 7.2, 5.0 Hz), 3.74 (1 H, d, *J* = 5.0 Hz), 7.13–7.23 (m, 5 H).

(2*S*,3*S*)-2,3-Dimethylphenylalanine (9b)[15b]

Mp 263–265 °C; $[\alpha]_D^{25}$ –31.42 (*c* 0.3472, MeOH) [Lit.[15b] –31.7 (*c* 0.492, MeOH)].

^{1}H NMR (DMSO-d_6/DCl): δ = 0.94 (3 H, d, *J* = 5.4 Hz), 1.07 (3 H, s), 2.95 (1 H, q, *J* = 5.6 Hz), 6.84–6.91 (5 H, m).

(2*R*,3*R*)-2,3-Dimethylphenylalanine

This compound was prepared according to the above procedures, starting form the complex **4b** derived from (*R*)-proline; $[\alpha]_D^{25}$ +31.38 (*c* 0.2679, MeOH)}

Acknowledgment

This work was supported by the Department of Chemistry and Biochemistry, University of Oklahoma and by the Undergraduate Research Opportunities Program, Honors College, University of Oklahoma. T.U.B. and S.B.B. thank Yamanouchi Pharma (currently Astellas), U.S.A., for generous fellowships. The authors gratefully acknowledge generous financial support from Central Glass Company (Tokyo, Japan) and Ajinomoto Company (Tokyo, Japan).

References

(1) As we recently pointed out (see ref. 2), the terms unnatural, unusual, or nonproteinogenic, noncoded amino acids depend on the success of specific scientific achievements. For instance, amino acids containing the most xenobiotic element fluorine were shown to be synthesized by microorganisms (see ref. 3), and also new amino acids can be added to genetic code of microorganisms (see ref. 4). Therefore, the time-independent term tailor-made, meaning rationally designed/synthesized amino acids, in the absence of a better definition, is used in this paper and generally recommended for use in the corresponding literature.

(2) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. *Tetrahedron* **1999**, *55*, 12045.

(3) (a) *Fluorine-Containing Amino Acids. Synthesis and Properties*; Kukhar', V. P.; Soloshonok, V. A., Eds.; Wiley: Chichester, **1994**. (b) O'Hagan, D.; Schaffrath, C.; Cobb, S.; Hamilton, J. T. G.; Murphy, C. D. *Nature* **2002**, *416*, 279.

(4) (a) Wang, L.; Brock, A.; Herberich, B.; Schultz, P. G. *Science* **2001**, *292*, 498. (b) Deiters, A.; Cropp, A. T.; Mukherji, M.; Chin, J. W.; Anderson, C. J.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782.

(5) Hruby, V. J.; Lu, G.; Haskell-Luevano, C.; Shenderovich, M. D. *Biopolymers (Peptide Science)* **1997**, *43*, 219; and references cited therein.

(6) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585; and references cited therein.

(7) For monographs, see: (a) *Molecular Conformation and Biological Interactions*; Balaram, P.; Ramaseshan, S., Eds.; Indian Academy of Science: Bangalore, **1991**. (b) *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; JAI Press Inc.: Greenwich, **1999**, 191–220.

(8) Special issue on *Protein Design*, Guest Editor DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3025–3032.

(9) For a recent collection of papers, see the Special Issue: *Asymmetric Synthesis of Novel Sterically Constrained Amino Acids*, Tetrahedron Symposia-in-Print # 88; Guest Editors Hruby, V. J.; Soloshonok, V. A. *Tetrahedron* **2001**, *57*, 6329–6650.

Downloaded by: University of Illinois. Copyrighted material.

(10) For general reviews on asymmetric synthesis of α-amino acids, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 654. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (d) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

(11) Gomez-Catalan, J.; Perez, J. J.; Jimenez, A. I.; Cativiela, C. *J. Pept. Sci.* **1999**, *5*, 251.

(12) (a) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (b) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147. (c) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153. (d) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438. (e) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820.

(13) (a) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548. (b) Ooi, T.; Uematsu, Y.; Fujimoto, J.; Fukumoto, K.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 1337. (c) Ooi, T.; Kato, D.; Inamura, K.; Ohmatsu, K.; Maruoka, K. .

(14) (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (b) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1115. (c) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708. (d) Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc.* **1994**, *116*, 7405.

(15) (a) Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796. (b) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559.

(16) (a) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (b) Kazmierski, W. M.; Urbanczyk-Lipkowska, Z.; Hruby, V. J. *J. Org. Chem.* **1994**, *59*, 1789.

(17) Soloshonok, V. A.; Tang, X.; Hruby, V. J.; Meervelt, L. V. *Org. Lett.* **2001**, *3*, 341.

(18) For selected recent reviews, see: (a) Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215. (b) Bouifraden, S.; Drouot, C.; El Hadrami, M.; Guenoun, F.; Lecointe, L.; Mai, N.; Paris, M.; Pothion, C.; Sadoune, M.; Sauvagnat, B.; Amblard, M.; Aubagnac, J. L.; Calmes, M.; Chevallet, P.; Daunis, J.; Enjal-bal, C.; Fehrentz, J. A.; Lamaty, F.; Lavergne, J. P.; Lazaro, R.; Rolland, V.; Roumestant, M. L.; Viallefont, P.; Vidal, Y.; Martinez, J. *Amino Acids* **1999**, *16*, 345. (c) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621. (d) Beller, M.; Eckert, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1010. (e) Kawabata, T.; Fuji, K. *Synth. Org. Chem. Jpn.* **2000**, *58*, 1095. (f) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523. (g) Yao, S. L.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. (h) Abellan, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689. (i) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197. (j) Shioiri, T.; Hamada, Y. *Synlett* **2001**, 184. (k) Williams, R. M. *Synthesis of Optically Active a-Amino Acids*; Pergamon Press: Oxford, **1989**.

(19) (a) Belokon, Y. N. *Janssen Chim. Acta* **1992**, *10 (2)*, 4. (b) Belokon, Y. N. *Pure Appl. Chem.* **1992**, *64*, 1917.

(20) Ueki, H.; Ellis, T. K.; Martin, C. H.; Bolene, S. B.; Boettiger, T. U.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7104.

(21) (a) Andronova, I. G.; Maleev, V. I.; Ragulin, V. V.; Il'in, M. M.; Tsvetkov, E. N.; Belokon', Yu. N. *Zh. Obshch. Khim.* **1996**, *66*, 1096. (b) Tararov, V. I.; Savel'eva, T. F.; Kuznetsov, N. Yu.; Ikonnikov, N. S.; Orlova, S. A.; Belokon', Yu. N.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 79. (c) Sagiyan, A. S.; Dzhamgaryan, S. M.; Grigoryan, G. L.; Kagramanyan, S. R.; Ovsepyan, G. Ts.; Grigoryan, S. K.; Belokon', Yu. N. *Khimich. Zh. Armenii* **1996**, *49*, 75. (d) Sagiyan, A. S.; Grigoryan, S. K.; Dzhamgaryan, S. M.; Grigoryan, G. L.; Belokon', Yu. N. *Khimich. Zh. Armenii* **1996**, *49*, 142. (e) Belokon', Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Strelkova, T. V.; Harutyunyan, S. R.; Saghiyan, A. S. *Tetrahedron: Asymmetry* **2001**, *12*, 481. (f) Larionov, O. V.; Savel'eva, T. F.; Kochetkov, K. A.; Ikonnokov, N. S.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Khrustalev, V. N.; Belokon, Y. N.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 869. (g) Belokon, Y. N.; Kochetkov, K. A.; Borkin, D. A. *Mendeleev Commun.* **2003**, 132. (h) Belokon, Y. N.; Maleev, V. I.; Savel'eva, T. F.; Moskalenko, M. A.; Pripadchev, D. A.; Khrustalev, V. N.; Vorontsov, E. V.; Sagiyan, A. S.; Babayan, E. P. *Russ. Chem. Bull.* **2005**, *54*, 981.

(22) (a) Soloshonok, V. A.; Belokon, Y. N.; Kukhar, V. P.; Chernoglazova, N. I.; Saporovskaya, M. B.; Bakhmutov, V. I.; Kolycheva, M. T.; Belikov, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 1630. (b) Soloshonok, V. A.; Kukhar, V. P.; Galushko, S. V.; Kolycheva, M. T.; Rozhenko, A. B.; Belokon, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, 1166. (c) Soloshonok, V. A.; Kukhar, V. P.; Batsanov, A. S.; Galakhov, M. A.; Belokon, Y. N.; Struchkov, Y. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, 1548. (d) Soloshonok, V. A.; Kukhar, V. P.; Galushko, S. V.; Rozhenko, A. B.; Kuzmina, N. A.; Kolycheva, M. T.; Belokon, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1991**, 1906. (e) Soloshonok, V. A.; Svistunova, N. Y.; Kukhar, V. P.; Gudima, A. O.; Kuzmina, N. A.; Belokon, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1992**, 117. (f) Soloshonok V. A., Svistunova N. Y., Kukhar V. P., Solodenko V. A., Kuzmina N. A., Rozhenko A. B., Galushko S. V., Shishkina I. P., Gudima A. O., Belokon Y. N.; *Izv. Akad. Nauk SSSR, Ser. Khim.*; **1992**, 397. (g) Soloshonok, V. A.; Svistunova, N. Y.; Kukhar, V. P.; Kuzmina, N. A.; Belokon, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1992**, 687. (h) Soloshonok, V. A.; Belokon, Y. N.; Kuzmina, N. A.; Maleev, V. I.; Svistunova, N. Y.; Solodenko, V. A.; Kukhar, V. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1525. (i) Kukhar, V. P.; Belokon, Y. N.; Svistunova, N. Y.; Soloshonok, V. A.; Rozhenko, A. B.; Kuzmina, N. A. *Synthesis* **1993**, 117. (j) Soloshonok, V. A.; Svistunova, N. Y.; Kukhar, V. P.; Kuzmina, N. A.; Popov, V. I.; Belokon, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1993**, 786. (k) Soloshonok, V. A.; Kukhar, V. P.; Galushko, S. V.; Svistunova, N. Y.; Avilov, D. V.; Kuzmina, N. A.; Raevski, N. I.; Struchkov, Y. T.; Pisarevsky, A. P.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3143. (l) Kukhar, V. P.; Luik, A. I.; Soloshonok, V. A.; Svistunova, N. Y.; Skryma, R. N.; Rybalchenko, V. V.; Belokon, Y. N.; Kuzmina, N. A. *Khim. Pharm. Zh.* **1994**, *27*, 35. (m) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Tararov, V. I.; Saveleva, T. F.; Churkina, T. D.; Ikonnikov, N. S.; Kochetkov, K. A.; Orlova, S. A.; Pysarevsky, A. P.; Struchkov, Y. T.; Raevsky, N. I.; Belokon, Y. N. *Tetrahedron: Asymmetry* **1995**, *6*, 1741. (n) Soloshonok, V. A.; Gerus, I. I.; Yagupolskii, Y. L.; Kukhar, V. P. *Zh. Org. Khim.* **1987**, *23*, 2308; *Chem. Abstr.* **1988**, *109*, 55185. (o) Basyuk, V. A.; Gromovoi, T. Y.; Chuiko, A. A.; Soloshonok, V. A.; Kukhar, V. P. *Synthesis* **1992**, 449.

Downloaded by: University of Illinois. Copyrighted material.

(23) (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron: Asymmetry* **1996**, *7*, 1547. (b) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 12433. (c) Soloshonok, V. A.; Avilov, D. V.; Kukhar', V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4671. (d) Soloshonok, V. A.; Avilov, D. V.; Kukhar', V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4903. (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Mischenko, N. *Tetrahedron* **1999**, *55*, 12031. (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V. *Tetrahedron* **1999**, *55*, 12045. (g) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4265. (h) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 135. (i) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747. (j) Qiu, W.; Soloshonok, V. A.; Cai, C.; Tang, X.; Hruby, V. J. *Tetrahedron* **2000**, *56*, 2577. (k) Soloshonok, V. A.; Cai, C.; Hruby, V. J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2172. (l) Tang, X.; Soloshonok, V. A.; Hruby, V. J. *Tetrahedron: Asymmetry* **2000**, *11*, 2917. (m) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688. (n) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 9645. (o) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339. (p) Soloshonok, V. A.; Tang, X.; Hruby, V. J. *Tetrahedron* **2001**, *57*, 6375. (q) Soloshonok, V. A. *Curr. Org. Chem.* **2002**, *6*, 341. (r) Ellis, T. K.; Hochla, V. M.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 4973. (s) Taylor, S. M.; Yamada, T.; Ueki, H.; Soloshonok, V. A. *Tetrahedron Lett.* **2004**, *45*, 9159. (t) Soloshonok, V. A.; Cai, C.; Yamada, T.; Ueki, H.; Ohfune, Y.; Hruby, V. J. *J. Am. Chem. Soc.* **2005**, *127*, 15296. (u) Soloshonok, V. A.; Yamada, T.; Ueki, H.; Moore, A. M.; Cook, T. K.; Arbogast, K. L.; Soloshonok, A. V.; Martin, C. H.; Ohfune, Y. *Tetrahedron* **2006**, *62*, 6412. (v) Soloshonok, V. A.; Ueki, H. *J. Am. Chem. Soc.* **2007**, *129*, 2426.

(24) (a) Fishwick, C. W. G.; Sanderson, J. M.; Findlay, J. B. C. *Tetrahedron Lett.* **1994**, *35*, 4611. (b) Chen, B.-H.; Nie, J.-Y.; Singh, M.; Pike, V. W.; Kirk, K. L. *J. Fluorine Chem.* **1995**, *75*, 93. (c) Kliukiene, R.; Maroziene, A.; Stumbreviciute, Z.; Karpavicius, K. *Chemija* **1996**, *3*, 76. (d) Mosevich, I. K.; Kuznetsova, O. F.; Fedorova, O. S.; Korsakov, M. V. *Radiochemistry (Moscow)* **1996**, *38*, 511. (e) Jirman, J.; Nadvornik, M.; Sopkova, J.; Popkov, A. *Magn. Reson. Chem.* **1998**, *36*, 351. (f) Collet, S.; Bauchat, P.; Danion-Bougot, R.; Danion, D. *Tetrahedron: Asymmetry* **1998**, *9*, 2121. (g) Popkov, A.; Jirman, J.; Nadvornik, M.; Manorik, P. A. *Collect. Czech. Chem. Commun.* **1998**, *63*, 990. (h) Popkov, A. N.; Nadvornik, M.; Iirman, I.; Sopkova, Ya.; Manorik, P. A.; Fedorenko, M. A. *Russ. J. Gen. Chem.* **1998**, *68*, 1242. (i) Mosevich, I. K.; Kuznetsova, O. F.; Vasil'ev, D. A.; Anichkov, A. A.; Korsakov, M. V. *Radiochemistry (Moscow)* **1999**, *41*, 273. (j) Collet, S.; Carreaux, F.; Boucher, J.-L.; Pethe, S.; Lepoivre, M.; Danion-Bougot, R.; Danion, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 177. (k) Debache, A.; Collet, S.; Bauchat, P.; Danion, D.; Euzenat, L.; Hercouet, A.; Carboni, B. *Tetrahedron: Asymmetry* **2001**, *12*, 761. (l) Nadvornik, M.; Popkov, A. *Green Chem.* **2002**, *4*, 71. (m) Gu, X.; Tang, X.; Cowell, S.; Ying, J.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 6669. (n) Hashimoto, M.; Hatanaka, Y.; Sadakane, Y.; Nabeta, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2507. (o) Zhang, J.; Xiong, C.; Ying, J.; Wang, W.; Hruby, V. J. *Org. Lett.* **2003**, *5*, 3115. (p) Chaykovski, M. M.; Bae, L. C.; Cheng, M.-C.; Murray, J. H.; Tortolani, K. E.; Zhang, R.; Seshadri, K.; Findlay, J. H. B. C.; Hsieh, S.-Y.; Kalverda, A. P.; Homans, S. W.; Brown, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 15767. (q) Gu, X.; Ndungu, J. M.; Qiu, W.; Ying, J.; Carducci, M. D.; Wooden, H.; Hruby, V. J. *Tetrahedron* **2004**, *60*, 8233. (r) Hao, B.; Zhao, G.; Kang, P. T.; Soares, J. A.; Ferguson, T. K.; Gallucci, J.; Krzycki, J. A.; Chan, M. K. *Chem. Biol.* **2004**, *11*, 1317. (s) Ouchi, H.; Kumagai, M.; Sakurada, S.; Takahata, H. *Heterocycles* **2004**, *64*, 505. (t) Ghalit, N.; Poot, A. J.; Fuerstner, A.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 2961. (u) Pessoa, J. C.; Correia, I.; Galvao, A.; Gameiro, A.; Felix, V.; Fiuza, E. *Dalton Trans.* **2005**, 2312. (v) Vadon-Legoff, S.; Dijols, S.; Mansuy, D.; Boucher, J.-L. *Org. Process Res. Dev.* **2005**, *9*, 677. (w) Popkov, A.; Cisarova, I.; Sopkova, J.; Jirman, J.; Lycka, A.; Kochetkov, K. A. *Collect. Czech. Chem. Commun* **2005**, *70*, 1397. (x) Saghiyan, A. S.; Dadayan, S. A.; Petrosyan, S. G.; Manasyan, L. L.; Geolchanyan, A. V.; Djamgaryan, S. M.; Andreasyan, S. A.; Maleev, V. I.; Khrustalev, V. N. *Tetrahedron: Asymmetry* **2006**, *17*, 455. (y) Saghiyan, A. S.; Geolchanyan, A. V. *Synth. Commun.* **2006**, *36*, 3667. (z) Langer, V.; Popkov, A.; Nadvornik, M.; Lycka, A. *Polyhedron* **2007**, *26*, 911.

(25) As shown previously (see refs. 21–23), CD and ORD spectra of Ni(II) complexes of this type in neutral solutions exhibit two maxima in the region of metal d-d transition (Cotton effects at 450 and 550 nm). In the ORD spectra, the sign of Cotton effects in this region strictly depends upon a conformation of the polycyclic system of chelate rings. Thus, in the case of complexes containing α-monosubstituted α-amino acid, the pseudoaxial orientation of the amino acid side chain, corresponding to α-L configuration of α-amino acid, causes a Cotton effect with a positive sign at the 500–700 nm region and negative sign at 400–450 nm. Consequently, a pseudoequatorial orientation of the amino acid side chain brings about opposite signs of the Cotton effects at 400–450 (positive) and at the 500–700 nm (negative) regions. As established in numerous studies, this general trend is not influenced by the structure and nature of the α-amino acid side chain, and the configuration of stereogenic centers within it.

(26) For the complex containing (2*S*,3*R*)-3-phenylglutamic acid, the α-proton appears at δ = 4.14 ($J_{\alpha H,\beta H}$ = 3.7 Hz); for the complex containing (2*S*,3*S*)-3-phenylglutamic acid, the α-proton is at δ = 4.07 ($J_{\alpha H,\beta H}$ = 7.0 Hz); for details, see: Belokon', Yu. N.; Bulychev, A. G.; Ryzhov, M. G.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Yu. T.; Bakhmutov, V. I.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1865.

(27) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733.

(28) (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4265. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 135. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747. (d) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2172. (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688. (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 9645. (g) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 1339. (h) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984. (i) Cai, C.; Yamada, T.; Tiwari, R.; Hruby, V. J.; Soloshonok, V. A. *Tetrahedron Lett.* **2004**, *45*, 6855. (j) Soloshonok, V. A.; Ueki, H.; Ellis, T. K. *Tetrahedron Lett.* **2005**, *46*, 941. (k) Soloshonok, V. A.; Ueki, H.; Ellis, T. K.; Yamada, T.; Ohfune, Y. *Tetrahedron Lett.* **2005**, *46*, 1107. (l) Soloshonok, V. A.; Ellis, T. K. *Synlett* **2006**, 533. (m) Ellis, T. K.; Ueki, H.; Yamada, T.; Ohfune, Y.; Soloshonok, V. A. *J. Org. Chem.* **2006**, *71*, 8572.

Downloaded by: University of Illinois. Copyrighted material.