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Asymmetric Synthesis of α,β-Dialkyl-α-phenylalanines via Direct Alkylation of a Chiral Alanine Derivative with Racemic α-Alkylbenzyl Bromides. A Case of High Enantiomer Differentiation at Room Temperature

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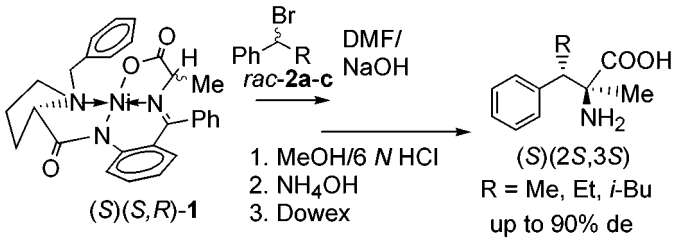
ABSTRACT



This study demonstrates that the direct alkylation of a Ni(II)-complex of the chiral Schiff base of alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]-benzophenone, with racemic α-alkylbenzyl bromides, is a synthetically feasible and methodologically advantageous approach to the target α,β-dialkylphenylalanines over previously reported methods. For the first time we report and rationalize a case of a high enantiomer differentiation process at room temperature.

α,β-Dialkyl-substituted α-amino acids are among the least studied, yet potentially very important class of tailor-made amino acids.[1,2] Analysis of the relevant literature,[3] including our own experience in *de novo* peptide design,[4] suggests that rational manipulation of the steric properties of the α- and β-alkyl groups in such amino acids might allow for a simultaneous control of the peptide backbone dihedral angles ϕ (phi), ψ (psi), and ω (omega) and the torsional angles (chi) χ^1, χ^2, etc., defining the position of side-chain functional groups.[3e,4a] Since all these dihedral angles are of key importance in determining the three-dimensional structure

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(1) For definition of "tailor-made amino acids", see footnote 2 in the following: Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. *Tetrahedron* **1999**, *55*, 12045.

(2) 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) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

(3) (a) *Molecular Conformation and Biological Interactions*; Balaram, P., Ramaseshan, S., Eds.; Indian Academy of Science: Bangalore, 1991. (b) Scheraga, H. A. *Chem. Rev.* **1971**, *71*, 195. (c) Ramachandran, G. N.; Sasisekharan, V. *Adv. Protein Chem.* **1968**, *23*, 283. (d) Bloom, S. M.; Fasman, G. D.; DeLoze, C.; Blout, E. R. *J. Am. Chem. Soc.* **1961**, *84*, 458. (e) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.

(4) (a) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolymers (Peptide Science)* **1997**, *43*, 219. (b) Hruby, V. J. *Life Sci.* **1982**, *31*, 189. (c) Nicolás, E.; Dharanipragada, R.; Tóth, G.; Hruby, V. J. *Tetrahedron Lett.* **1989**, *30*, 6841. (d) Hruby, V. J.; Slate, C. In *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; JAI Press Inc.: Greenwich, 1999; pp 191−220.

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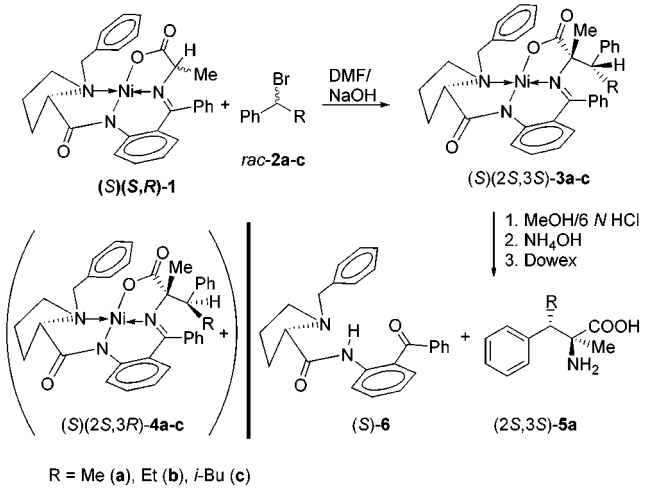
of peptides and, thus, their mode of biological action, incorporation of sterically defined α,*β*-dialkyl-substituted α-amino acids into peptides would provide a powerful tool for exploration of peptide-mediated biological information transfer.[3,4]

Asymmetric synthesis of the target amino acids is virtually undeveloped, however.[2] To the best of our knowledge only a recent report by the Davis group offers a relatively generalized approach to α,*β*-dialkyl-substituted α-amino acids via stepwise introduction of the required functionalities.[5] A more methodologically concise approach to the target amino acids would be by direct alkylation of chiral derivatives of alanine with racemic *sec*-alkyl halides.[6] In this Letter, we report the reactions between a chiral Ni(II)-complex of alanine (*S*)(*S*,*R*)-**1**[7] (Scheme 1) with a series of

Scheme 1



racemic 1-bromo-1-phenylalkanes **2a**−**c**,[8] which provide a fast, generalized, and synthetically efficient access to the target α,*β*-dialkyl-substituted α-amino acids.

A central issue for the stereochemical outcome of the reactions between chiral derivatives of alanine with racemic *sec*-alkyl halides is the enantiomer-differentiating ability of the former. A handful of reports describing high enantiomer-differentiation in the reactions between chiral derivatives of alanine[6] or glycine[9] utilized reactions conducted at low temperatures (−78 °C). Therefore, we were most interested in developing a process which could be conducted at synthetically more convenient, higher temperatures, ultimately, room-temperature reactions.

The alkylations of the alanine complex (*S*)(*S*,*R*)-**1**[10] with *rac*-**2a**−**c** (ratio 1/2.5, respectively) were conducted under our standard conditions: in DMF solutions using powdered NaOH as a base. The temperature of the reactions was varied to study its influence on the stereochemical outcome. The results obtained are given in Table 1. First of all, we were

Table 1. Reactions of (*S*)(*S*,*R*)-**1** with **2a**−**c**[a]

entry	**2a**−**c**	*T*, °C	time, min	yield,[b] %	ratio[c] **3**/**4**
1	**a**	25	60	92	5.7/1[d]
2	**a**	0	90	94	6.2/1
3	**a**	−10	140	94	19.0/1
4	**b**	25	40	90	14.9/1
5	**b**	−10	140	97	17.0/1
6	**c**	25	240	90	3.0/1
7	**c**	0	360	93	6.0/1
8	**c**	−10	480	90	12.0/1

[a] All reactions were run under an oxygen-free nitrogen atmosphere. Ratio (*S*)(*S*,*R*)-**1**/**2a**−**c** was 1/2.5. [b] Combined yield of all diastereomeric products. [c] Ratio of diastereomeric products (*S*)(2*S*,3*R*)-3/(*S*)(2*S*,3*S*)-**4** was determined on the crude reaction mixtures by ^{1}H NMR (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] Some amounts (<5%) of (2*R*)-configured product also were detected in the reaction mixture.

pleased to find that even at room temperature (25 °C) the alkylation of the alanine complex (*S*)(*S*,*R*)-**1** with racemic α-methylbenzyl bromide (**2a**) occurred with substantial stereoselectivity, giving rise to a mixture of diastereomeric products (*S*)(2*S*,3*S*)-**3a** and (*S*)(2*S*,3*R*)-**4a** in a ratio of 5.7 to 1 (entry 1). Lowering the reaction temperature expectedly decreased the rate of the alkylation (entries 2 and 3 vs 1) but noticeably increased the enantiomer stereodifferentiation process allowing preparation of (*S*)(2*S*,3*S*)-**3a** with synthetically meaningful diastereoselectivity (90% de) (entry 3). The major product (*S*)(2*S*,3*S*)-**3a** was isolated in diastereomerically pure form simply by washing the reaction mixture with diethyl ether and was decomposed to give the target (2*S*,3*S*)-α,*β*-dimethylphenylalanine (**5a**) in 70% overall yield, along with the recovered chiral ligand (*S*)-**6**[11] (96%) (Scheme 1). Alkylation of alanine complex (*S*)(*S*,*R*)-**1** at room temperature with the more sterically demanding α-ethylbenzyl bromide (**2b**) gave more impressive results, affording the major product (*S*)(2*S*,3*S*)-**3** with 93.7% diastereoselectivity (entry 4 vs 1). As observed in the reaction between (*S*)(*S*,*R*)-**1** with **2a** (entries 1−3), lowering the temperature (−10 °C) increased the selectivity of the enantiomer differentiation process in the alkylation of (*S*)(*S*,*R*)-**1** with **2b** (entry 5). However, the observed diastereoselectivity was lower than that obtained in the reaction between (*S*)(*S*,*R*)-**1** and **2a** (entry 5 vs 3). Unexpectedly, a further increase in the steric bulk of the alkylating agent resulted in decreased diastereoselectivity. Thus, alkylation of (*S*)(*S*,*R*)-**1** with α-isobutylbenzyl

(5) (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.

(6) Kazmierski, W. M.; Urbanczyk-Lipkowska, Z.; Hruby, V. J. *J. Org. Chem.* **1994**, *59*, 1789.

(7) A Ni(II)-complex of the chiral Schiff base of alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (**1**) was available from a previous study: Qiu, W.; Soloshonok, V. A.; Cai, C.; Tang, X.; Hruby, V. J. *Tetrahedron* **2000**, *56*, 2577.

(8) *rac*-1-Bromo-1-phenylethane (**1a**) is commercially available; the other 1-bromo-1-phenylalkanes (**1b**,**c**) were prepared by dehydroxybromination of the corresponding benzylic alcohols; see the Supporting Information.

(9) (a) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (b) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, 1337.

(10) Complex **1** prepared from racemic alanine and chiral ligand (*S*)-**6** (see Scheme 1) was obtained and used as a mixture of (*S*)(α-*S*) and (*S*)-(α-*R*) diastereomers in a ratio of 9 to 1.

(11) Ligand (*S*)-**6**, isolated stereochemically intact, was readily transformed to the starting Ni(II)-complex (*S*)(*S*,*R*)-**1**.

bromide (**2c**) at room temperature gave a mixture of the corresponding diastereomeric products (2*S*,3*S*)-**3a** and (*S*)-(2*S*,3*R*)-**4a** in a ratio of 3:1, respectively (entry 6). While a decrease of the reaction temperature allowed us to reach a respectable level of diastereoselectivity (92.3%) (entries 7 and 8), the results of the enantiomer differentiation process obtained in this series were noticeably lower as compared with the data observed in the alkylations of (*S*)(*S*,*R*)-**1** with **2a**,**b** (entries 6−8 vs 1−3 and 4 and 5). These data allow us to arrive at the surprising conclusion that an increase in the steric bulk of the alkylating agents **2a**−**c** results in a lowering of the enantiomer differentiation selectivity. On the other hand, the high level of the diastereoselectivity, especially at room temperature, observed in the reactions suggests that the present methodology is definitely synthetically superior to the previously described methods, providing a reliable access to this family of α,*β*-dialkyl amino acids.

The absolute configuration of the α-stereogenic center of the newly formed amino acids in products **3** and **4** was determined to be (*S*) on the basis of their chiroptical properties and NMR data.[12] Accordingly, complexes **3** and **4** could be considered as diastereomers, differing in the absolute configuration at the *β*-stereogenic center. It follows that attack by the alkylating agent **2a**−**c** occurs almost exclusively[13] on the *si*-face of the enolate derived from the complex **1**. As mentioned above, decomposition of the complex **3a** to the free amino acid (2*S*,3*S*)-**5a** allowed us to determine the (2*S*,3*S*) stereochemistry of the former. Moreover, taking into account the surprising observation that an increase in the steric bulk of the alkylating agent reduced the stereodifferentiation between the enantiomers of **2a**−**c**, we performed single-crystal X-ray analysis of the major product **3b** obtained in the reaction between (*S*)(*S*,*R*)-**1** and **2b** which confirmed its (2*S*,3*S*) absolute configuration. On the basis of the obvious similarity in the ^{1}H NMR spectra between **3a**,**b** and **3c**, and on the other hand between **4a**,**b** and **4c**, we confidently assigned a (2*S*,3*S*)-configuration to **3c** and a (2*S*,3*R*) stereochemistry to **4c**.

With the assigned stereochemistry of the products, we are in position to discuss the mechanism of these alkylation reactions. Considering the three possible transition states (TSs) **A**−**C** (Figure 1), with the approach geometry *unlike*, leading to the products of (2*S*,3*S*) absolute configuration **3a**−**c**, and the three TSs **D**−**F**, of approach geometry *like*, affording the (*S*)(2*S*,3*R*) configured products **4a**−**c**, we suggest that the TSs **A** and **F** are the most plausible to account for the formation of products (*S*)(2*S*,3*S*)-**3a**−**c** and (*S*)(2*S*,3*R*)-**4a**−**c**, respectively. Thus, in the TSs **A** and **F** the phenyl of the alkylating agent occupies the position of the largest group, avoiding unfavorable steric interactions with the ketimine phenyl and the Ni atom of the alanine complex (TSs **A** and **F** vs **B**−**E**). On the other hand, TS **A** should be regarded more thermodynamically favorable relative to **F**, as in the latter the substituent R experiences a direct unfavorable nonbonding steric interaction with the ketimine phenyl of the complex. Moreover, TS **A** perfectly accounts for the unexpected observation that an increase in the steric bulk of the substituent R interferes with a high level of an enantiomer differentiation process. Thus, in TS **A** the substituent R points directly to the Ni ion and, as one can expect, increases in the steric bulk of R would bring correspondingly unfavorable nonbonding interactions destabilizing TS **A**. On the basis of the results obtained, we conclude that while the steric bulk of methyl and ethyl groups could be accommodated by TS **A**, the stereochemical requirements of the isobutyl substituent are definitely larger, decreasing the thermodynamic difference between TSs **A** and **F**.

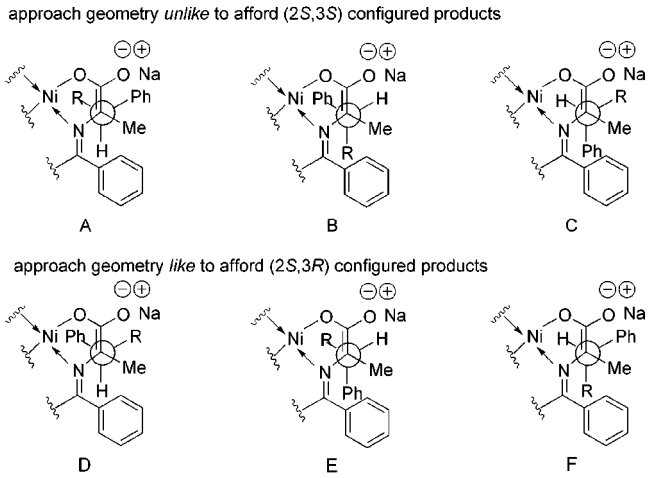


Figure 1. Possible TSs in the reactions between (*S*,*R*)-**1** and **2a**−**c**.

In summary, this study has demonstrated that direct alkylation of alanine complex (*S*)(*S*,*R*)-**1** with racemic **2a**−**c** is a synthetically feasible and methodologically advantageous approach to the target α,*β*-dialkylphenylalanines over the previously reported methods.[2,5] For the first time we report and rationalize a case of a high enantiomer differentiation process at room temperature. Because of the simplicity of the experimental procedure, the low cost of the required reagents, and the high chemical and optical yields of the targeted products, this method is immediately useful for preparing α,*β*-dialkyl-substituted α-amino acids.

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Supporting Information Available: Experimental procedures and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000330O

(12) For details on determination of the absolute configuration of the α-stereogenic center in complexes of type **3** and **4**, see: Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Mischenko, N. *Tetrahedron* **1999**, *55*, 12031.

(13) See footnote d in Table 1.