Organic Chemistry

Asymmetric alkylation catalyzed by chiral alkali metal alkoxides of TADDOL. Synthesis of α-methyl amino acids

Yu. N. Belokon',[a] K. A. Kochetkov,[a] T. D. Churkina,[a] N. S. Ikonnikov,[a] A. A. Chesnokov,[b] O. V. Larionov,[b] and H. V. Kagan[c]*

[a]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation. Fax: +7 (095) 135 5085. E-mail: yubel@ineos.ac.ru
[b]Higher Chemical College, Russian Academy of Sciences, 9 Miusskaya pl., 125820 Moscow, Russian Federation. Fax: +7 (095) 200 4204
[c]Institut de Chimie Moleculaire d'Orsay, Universite de Paris Sud. 91405, Orsay Cedex, URA CNRS 1497, France

It is shown that sodium alkoxides formed from (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol) ((*R*,*R*)-TADDOL) and some of its derivatives can be used as chiral catalysts for enantioselective alkylation of Schiff's bases derived from alanine with reactive alkyl halides. Acid hydrolysis of the reaction products affords (*R*)-α-methylphenylalanine, (*R*)-α-allylalanine, and (*R*)-α-methylnaphthylalanine in 61—93% yields and with *ee* 69—94%. When (*S*,*S*)-TADDOL is used, the (*S*)-amino acid is formed. A mechanism explaining the observed features of the reaction is proposed.

Key words: asymmetric reaction, enantioselectivity, alcoholates of chiral diols, chiral catalysts, (4*R*,5*R*)- and (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol), (*R*)- and (*S*)-α-methyl amino acids.

Among the methods of catalytic asymmetric alkylation of CH acids, practically feasible chiral phase transfer catalysis seems quite promising; however, its enantioselectivity is normally relatively low.[1,2] Only the use of quaternary ammonium salts based on cinchonidine provides high (>90%) *ee* values for a narrow range of substances.[3] The few successful studies published in recent years in fact make use of modification of the known catalysts.[4—6] Unfortunately, these ammonium salts are unstable in the presence of alkali and decompose to give achiral derivatives, which also promote the reaction, which results in the formation of a racemic product and decreases the process enantioselectivity.[7] Thus, the search for new chiral catalysts of alkylation is quite topical.

α-Methyl amino acids (Me-AA) play an important role in natural processes and present interest for biology.[8,9] For instance, α-allyl-α-alanine (α-All-Ala) and α-methylnaphthylalanine (α-Me-Naphth-Ala) are valuable nonprotein amino acids[1,2,8,9]; (*S*)-α-methylphenylalanine ((*S*)-α-Me-Phe) is a very important compound for the synthesis of aspartam derivatives.[10] Modern analysis of the pathways leading to α-Me-AA sets development of catalytic methods as a primary task.[10] In the

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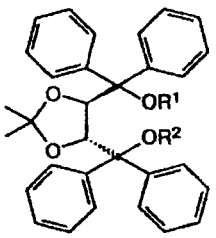
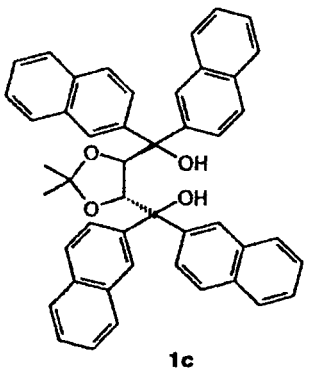
present study, we propose a new phase transfer catalyst for asymmetric alkylation of Schiff's bases derived from esters of DL-Ala, namely, an available chiral diol, (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol) (TADDOL, **1a**).[11,12] The use of this catalyst has been briefly reported in our previous communication.[13]

Recently, we used for the first time TADDOL alcoholates as catalysts of the asymmetric Michael reaction, namely, the 1,4-addition of the glycine synthon to methyl methacrylate and methyl acrylate.[14,15] In the enantioselective alkylation of CH acids containing a carboxy group, previously, alcohols have been used as chiral reagents only in equimolar amounts, needed for the formation of intermediate compounds, esters, which were then subjected to alkylation.[16]



1a,b,d

a: $R^1 = R^2 = H$
b: R^1 = Bn, $R^2 = H$
d: $R^1 = R^2$ = Me



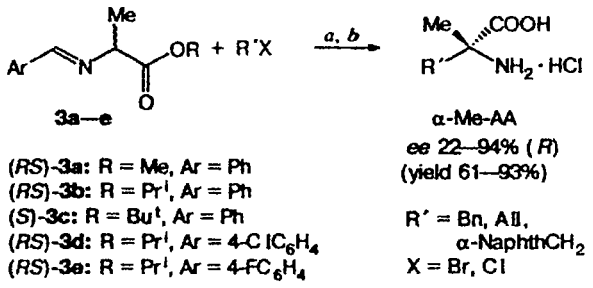
1c

(*RS*)-**2**

As the first substrate, we used racemic complex **2**. The product of alkylation of complex **2** cannot undergo epimerization; therefore, the ratio of enantiomers obtained in the reaction reflects the actual kinetic stereoselectivity of the process. In addition, the C—H bond in the alanine fragment is activated; this fragment possesses a high CH acidity (for complexes of this type, pK_a ~19, DMSO).[17] Thus, compound **2** can be readily alkylated at the α-carbon atom using alkali or alkoxides as bases.[18,19] Other studied substrates, Schiff's bases formed by DL-Ala and benzaldehyde (**3a—e**), also possess high CH acidities (pK_a ~20, DMSO)[20] and can be alkylated in the presence of alkali.[1,2]

Substrates **2** and **3** were alkylated in toluene at 15—20 °C in the presence of NaOH as a base and TADDOL (**1a**) or its derivatives and analogs (**1b—d**) taken in stoichiometric or catalytic amounts as chiral promoters (Scheme 1).

Scheme 1



3a—e

(*RS*)-**3a**: R = Me, Ar = Ph
(*RS*)-**3b**: R = Pr^i, Ar = Ph
(*S*)-**3c**: R = Bu^t, Ar = Ph
(*RS*)-**3d**: R = Pr^i, Ar = 4-C$_6$H$_4$Cl
(*RS*)-**3e**: R = Pr^i, Ar = 4-FC$_6$H$_4$

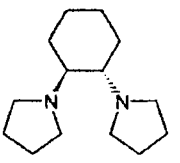
α-Me-AA
ee 22—94% (*R*)
(yield 61—93%)

R' = Bn, All, α-NaphthCH$_2$
X = Br, Cl

Reagents and conditions: *a*. NaOH (4—5 equiv.), (*R*,*R*)-TADDOL (**1a**) (0.1—1.0 equiv.), toluene, argon, 15—20 °C, 12 h; *b*. 6 *N* HCl(aq), 20 °C, 1 h, extraction of TADDOL, refluxing for 5 h.

The reaction product was decomposed under mild conditions to give α-Me-AA hydrochlorides, which were analyzed, after derivatization, by GLC on a chiral stationary phase (Table 1). It can be seen from Table 1 that TADDOL efficiently promotes asymmetric benzylation of substrates **2** and **3a—e** (entries *1—3*, *8*, *9*, *20* and *21*) with *ee* ranging from 20 to 94%. On passing to catalytic amounts, the yields and enantiomeric purity of products virtually do not change (*cf.* entries *3* and *4*). The high yields and *ee* values obtained in the catalytic experiments indicate that no enantiomeric enrichment of the reaction products induced by TADDOL occurs during their isolation. In fact, this enrichment does not occur when racemic products are mixed with TADDOL under the experimental conditions or during the subsequent workup.

Monobenzyl ether of TADDOL (**1b**) and the naphthyl analog of TADDOL (**1c**) also catalyze the reaction but the asymmetric induction is substantially lower (see Table 1, runs *13*, *14*). Diethyl tartrate or (*S*)-1,1'-bis(2-naphthol) do not catalyze alkylation of these substrates. Dimethyl ether of TADDOL (**1d**) (entry *15*) and diamine **4**, as well as 1,2-diols such as (+)-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**5**) and (*S*)-1-isopropyl-2,2-diphenylethane-1,2-diol (**6**) do catalyze the reaction but cause no asymmetric induction. For other 1,4-diols, the asymmetric induction observed under standard reaction conditions is relatively low: in the case of (+)-2,3-*O*-isopropylidene-L-threitol (unsubstituted analog of TADDOL) (**7**), the *ee* amounts to 15%, and for (+)-1,3:4,6-di-*O*-benzylidene-D-mannitol (**8**), this value is 6%.



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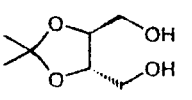

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Table 1. Benzylation of compounds **2** and **3a—e** by BnBr in the presence of compounds **1a—d** and a base[a]

Entry	Substrate	R	Amount of (*R,R*)-**1** /equiv.	Base (4 equiv.) + additives (0.1 equiv.)	Yield of α-Me-AA[b] (%)	*ee*[c] (*R*)-α-Me-AA (%)
1	**2**	—	1.0 (**1a**)	NaOH (Reachim)	85	20
2	**3a**	Me	1.0 (**1a**)	The same	0	—
3	**3b**	Pr^i	1.0 (**1a**)	The same	80	82
4	**3b**	Pr^i	0.1 (**1a**)	The same	81	82[d]
5	**3b**	Pr^i	0.1 (**1a**)	NaOH (Merck)	83	84
6	**3b**[e]	Pr^i	0.1 (**1a**)	NaOH (Reachim)	92	80
7	**3b**[f]	Pr^i	0.1 (**1a**)	The same	61	96
8	**3d**	Pr^i	0.1 (**1a**)	The same	89	83
9	**3e**	Pr^i	0.1 (**1a**)	The same	91	83
10	**3b**[g]	Pr^i	0.1 (**1a**)	The same	33	79
11	**3b**	Pr^i	0.1 (**1a**)	NaOH + + TMEDA	78	30
12	**3b**	Pr^i	0.1 (**1a**)	NaOH + + Et_4NBr	83	0
13	**3b**	Pr^i	1.0 (**1b**)	The same	68	3
14	**3b**	Pr^i	0.1 (**1c**)	The same	90	59
15	**3b**	Pr^i	0.1 (**1d**)	The same	60	2.5
16	**3b**	Pr^i	0.1 (**1a**)	NaOH (1 equiv.) + + H_2O	79	0
17	**3b**	Pr^i	0.1 (**1a**)	NaOH + + Na_2CO_3	65	21
18	**3b**	Pr^i	1.0 (**1a**)	KOH	31	24
19	**3b**	Pr^i	1.0 (**1a**)	LiOH	0	—
20	**3b**	Pr^i	1.0 (**1a**)	CsOH	94	0
21	**3c**[h]	Bu^t	1.0 (**1a**)	NaOH	45	38
22	**3c**[h]	Bu^t	0.1 (**1a**)	NaOH	93	22

[a] Reaction conditions: the molar ratio **2** (or **3a—c**) : : BnBr : **1a—d** : NaOH = 1.0 : 1.2 : (0.1—1.0) : (4.0—5.0), solvent PhMe, 15—20 °C; duration of the reaction was 12 h.
[b] Determined by ^1H NMR spectroscopy using Leu as the internal standard.
[c] Enantiomeric purity.
[d] After crystallization, the yield was 40% with an enantiomeric purity of more than 99%.
[e] In hexane.
[f] BnCl was used.
[g] The experiment with filtration of the catalyst (see Results and Discussion).
[h] Duration of the reaction was 7 days.

The reaction enantioselectivity markedly depends on the substrate structure. In the case of compound **2**, the *ee* value does not exceed 20%, while the yield of the product is high (see Table 1, entry *1*). For Schiff's base **3b**, the *ee* value increases to 84%, (entry *5*). Compound **3a** is rapidly hydrolyzed under the reaction conditions when NaOH is used as the base (entry *2*). Unexpectedly, Schiff's base **3c** proved to be a low-reactivity substrate, giving the final product with a low *ee* value (entries *21*, *22*). The replacement of the compound **3b** by its analogs, **3d,e**, does not influence the reaction outcome (entries *8*, *9*). It can be seen from the data presented in Table 1 that TADDOL catalyzes the reaction when introduced in a proportion of 10 mol.% with respect to the substrate (entries *4—12*).

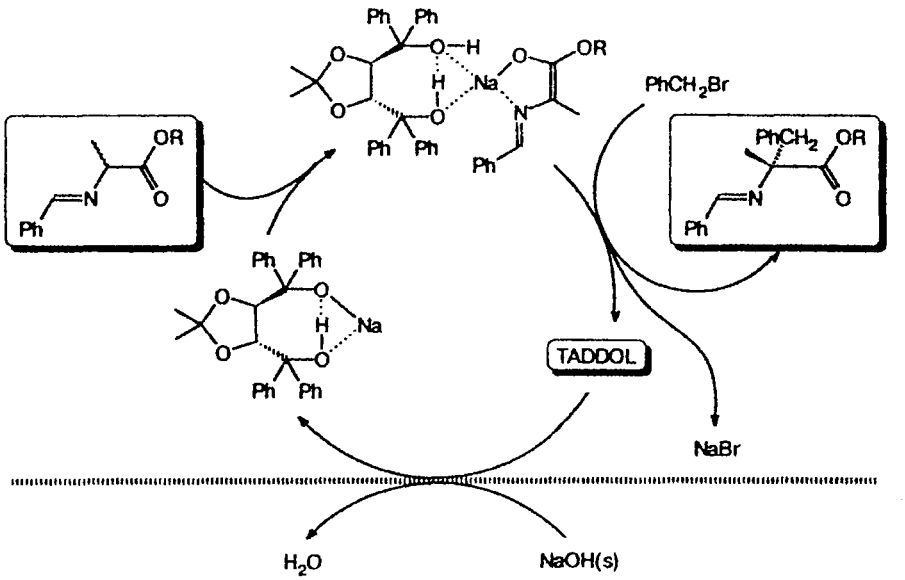
The type of the base used is significant because it is the base that stipulates the nature of the metal cation. For example, LiOH (see Table 1, entry *19*) is virtually inert, CsOH (entry *20*) gives rise to a racemic product, and in the case of KOH (entry *18*), a product with a low *ee* is formed. The use of Na_2CO_3 also sharply decreases *ee* (entry *17*).

Experiments on the extraction of metal picrates[13] showed that TADDOL exhibits properties of a phase transfer agent. Presumably, in the alkylation reaction considered here, it acts as a chiral hydrophobic phase transfer catalyst,[13] which forms a complex with the contact ion pair consisting of the enolate of **3** and a metal cation and thus promotes its transfer to the organic phase, in which alkylation by RX takes place. Yet another possible mechanism[13] assumes ionization of the diol on treatment with alkali, *i.e.*, functioning of the TADDOL alcoholate as a chiral base.

To elucidate the mechanism more precisely, we carried out a series of experiments that differed from the standard procedure[13] in the order of addition of the components. TADDOL and NaOH in toluene were placed in a dry flask filled with argon and stirred. As this was done, deprotonation induced by the base gave the corresponding alcoholate as a heterogeneous mixture, which was filtered in a flow of argon to remove excess solid alkali. Substrate **3b** and BnBr were added successively in a flow of argon to the resulting homogeneous solution, which can contain only TADDOL and/or the alcoholate. After stirring and the standard workup, (*R*)-α-Me-Phe was isolated in 33% yield with *ee* 79% (see Table 1, entry *10*). This means that the solution obtained after filtration contained the alcoholate of TADDOL, which catalyzed enantioselective alkylation of the substrate. In fact, the rigid structure of this diol is favorable for the complex formation with the cation. Finally, an intramolecular hydrogen bond between the ionized substrate and the diol can stabilize the complex with the ion pair formed by the enolate.

The following mechanism of the catalytic action of TADDOL can be proposed (Scheme 2). Apparently, hydrophobic TADDOL is ionized on treatment with solid alkali, and the alcoholate thus formed acts as a chiral base in an organic solvent, detaching the α-proton from the CH acid. The chiral ion pair consisting of the substrate enolate and the diol complexed with a metal ion is the intermediate species that undergoes alkylation. In the absence of TADDOL, alkylation hardly occurs, because the hydrophobic complex able to transfer the enolate of the substrate to the organic phase, containing RX, is not formed. In reality, the same intermediate complex is formed, irrespective of whether reaction involves the alcoholate of TADDOL acting as a hydrophobic base or the neutral diol exhibiting chelating

Scheme 2



properties and functioning similarly to other known chiral catalysts of alkylation of Li enolates.[21,22] After the complex has been alkylated, the diol is released to participate in a new catalytic cycle. The observed high enantioselectivity may be due not only to the high symmetry of TADDOL but also to the formation of an intramolecular hydrogen bond in the intermediate complex (see Scheme 2).

The absence of the products of *O*-alkylation of the diol in the reaction mixture, despite the presence of the alcoholate in the solution, can be attributed to the steric hindrance to the reaction. This permits TADDOL to be recovered after the process. The fact that TADDOL is difficult to alkylate is confirmed by the following experiment: even prolonged refluxing with excess BnBr in MeCN resulted only in the product of TADDOL monoalkylation, compound **1b**.

The addition of other compounds capable of chelating or transferring a carbanion owing to its hydrophobic properties (such as TMEDA, Et_4NBr), also facilitates this reaction and, correspondingly, decreases the enantioselectivity (see Table 1, entries *11*, *12*). The presence of an additional amount of water, which competes with the diol for chelation of the metal ion, also sharply decreases the *ee* value (entry *16*).

The enantioselectivity of the reaction depends appreciably on the structure of the substrate (**2** or **3**). We attribute this dependence to the fact that the enolate of substrate **2** can be coordinated to TADDOL only as a monodentate ligand, which does not suffice for rigid binding to the ion pair of enolate **2**. Apparently, in this case, the *pro-si*-face of the enolate is shielded only slightly, which results in low enantioselectivity of the reaction. Meanwhile, the enolates of substrates **3**, able to chelate sodium ions as bidentate ligands when binding to TADDOL, ensure a higher rigidity of this complex and, correspondingly, more pronounced shielding of one face (the *si*-face in the case of (4*R*,5*R*)-**1a**)) of the enolate against attack by the electrophile (see Scheme 2).

Methylation of the Schiff's base formed by the isopropyl ester of DL-phenylalanine (DL-Phe-OPr^i) (**3f**) by a small-size reagent (MeI) under the same conditions results not only in a lower yield of (*R*)-α-Me-Phe but also in a nearly lacking enantioselectivity (*ee* ~4%), similarly to the methylation of Schiff's bases in Ni^{II} complexes.[23] The low *ee* value in the final product in the case of substrate **3c** containing a Bu^t group can be due to steric restrictions hampering the formation of the complex of the enolate ion pair with TADDOL or to the competing spontaneous alkylation of the hydrophobic sodium salt of compound **3c**, which is correspondingly more soluble in toluene. The nature of the leaving group also influences the enantioselectivity. Thus when BnCl is used (see Table 1, entry *7*) instead of BnBr, the *ee* value increases from 84 to 96%; in terms of the proposed mechanism, this corresponds to the formation of a more structured transition state with the substrate ion pair in the nonpolar solvent.

Other active alkylating reagents, allyl bromide and α-naphthylmethyl chloride, also react efficiently with compound **3b** (Table 2, entries *1*—*5*) to give, after hydrolysis, (*R*)-α-All-Ala and (*R*)-α-Me-Naphth-Ala with *ee* 69—73 %. When (*R*,*R*)-TADDOL is used, the reaction affords (*R*)-α-Me-AA, whereas the use of (*S*,*S*)-TADDOL gives rise to (*S*)-α-Me-AA (entries *1*, *2*). Alkylation by low-reactivity reagents is inefficient (entry *6*).

Table 2. Alkylation of Schiff's bases **3b** in the presence of **1a** and NaOH[a]

Entry	RX	Amount of (*R,R*)-**1a** /mol	Yield of α-Me-AA[b] (%)	*ee*[c] (*R*)-α-Me-AA (%)	(*R*)-α-Me-AA
1	BnBr	0.1	81	82[d]	(*R*)-α-Me-Phe
2	BnBr	0.1[e]	81	82	(*S*)-α-Me-Phe
3	AllBr	1.0	91	73	(*R*)-α-All-Ala
4	AllBr	0.1	89	69	(*R*)-α-All-Ala
5	α-NaphthCH$_2$Cl	0.1	86	71	(*R*)-α-Me-Naphth-Ala
6	Pr^{i}Br	0.1	25	12	(*R*)-α-Me-Val

[a] For reaction conditions, see Table 1.
[b] Determined by ^{1}H NMR spectroscopy using Leu as the internal standard.
[c] Enantiomeric purity.
[d] After crystallization, the yield was 40% with an enantiomeric purity of more than 99%.
[e] (*S,S*)-**1a**.

Thus, we propose a new type of efficient catalysts for asymmetric *C*-alkylation of CH acids under conditions of phase transfer catalysis (PTC). The advantages of this approach over the known methods of asymmetric PTC alkylation[1–7,10,18] are stability and high enantioselectivity of the catalyst. TADDOL and its derivatives are highly stable, readily available,[11,12] and easily modifiable.[24] We believe that further increase in the number of chelating catalysts would allow the enantioselectivity of this reaction to be increased.

Experimental

^{1}H NMR spectra were recorded on a Bruker WP-200 instrument (200 MHz) using C_6D_6 as the external standard. The optical rotation was measured on a Perkin—Elmer 241 polarimeter. Electronic absorption spectra were recorded on a Specord M-40 instrument. Enantiomeric GLC analysis[25] of (a) (*R*)-α-Me-Phe, (b) (*R*)-α-All-Ala, and (c) (*R*)-α-Me-Naphth-Ala (a Chirasil-Val type phase*; a 32 m × 0.24 mm quartz capillary column; phase film thickness 0.12 mm; T = 165 °C (a), 75 °C (b), 190 °C (c); He as the carrier gas (pressure 1.8 bar)) was carried out for *n*-propyl esters of *N*-trifluoroacetyl derivatives of amino acids on a 3700-00 chromatograph (the Khromatograph plant, Moscow).

(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol) ((4*R*,5*R*)-TADDOL, **1a**) and (4*S*,5*S*)-TADDOL ((*S,S*)-**1a**) were synthesized by previously described procedures.[11,12] Diamine **4** was prepared by a known method.[26] Commercial diols **5**—**8** (Merck) and (−)-2,3-*O*-isopropylidene-1,1,4,4-tetra(2-naphthyl)-L-threitol (**1c**) (Fluka) were used.

Hexane and toluene were distilled from Na prior to the reaction (the water content was ≤0.01%; determined by the Fischer method at the analytical laboratory of the Institute of Organoelement Compounds). Granules of NaOH (Reakhim or Merck) were powdered in a glove box filled with Ar immediately prior to the reaction.

Complex of the Schiff's base formed by DL-Ala and *N*-(2-pyridylcarbonyl)-*o*-aminobenzaldehyde with Ni^{II} (2) was prepared by a previously described procedure,[18] m.p. 286 °C (decomp.). Found (%): C, 53.83; H, 3.57; N, 11.85. $C_{16}H_{13}N_3NiO_3$. Calculated (%): C, 54.29; H, 3.70; N, 11.87.

Schiff's bases **3a—f** were synthesized by standard procedures[27] from benzaldehyde and the corresponding Ala ester.

***N*-Benzylidene-DL-Ala methyl ester (3a).** Yield 66%, b.p. 112—113 °C (2.5 Torr) (Ref. 27: b.p. 105—107 °C (2 Torr)), n_D^{15} 1.5378. Found (%): C, 68.30; H, 6.82; N, 8.19. $C_{11}H_{13}NO_2$. Calculated (%): C, 69.09; H, 6.85; N, 7.32. ^{1}H NMR ($CDCl_3$), δ: 1.08 (d, 3 H, Me, J = 7.0 Hz); 3.29 (s, 3 H, OMe); 3.80 (q, 1 H, CH, J = 7.0 Hz); 6.60—7.30 (m, 5 H, Ph); 7.86 (s, 1 H, CH=N). IR, ν/cm^{-1}: 1451, 1581, 1643 (C=N); 1742 (C=O); 2952.

***N*-Benzylidene-DL-Ala isopropyl ester (3b).** Yield 71%, b.p. 120—121 °C (2 Torr), n_D^{15} 1.5168. Found (%): C, 71.18; H, 7.82; N, 6.55. $C_{13}H_{17}NO_2$. Calculated (%): C, 71.21; H, 7.81; N, 6.39. ^{1}H NMR ($CDCl_3$), δ: 1.23, 1.27 (both d, both 3 H, 2 Me, both J = 6.2 Hz); 1.51 (d, 3 H, Me, J = 7.1 Hz); 3.29 (q, 1 H, CH, J = 7.1 Hz); 3.80 (m, 1 H, OCH); 6.60—7.30 (m, 5 H, Ph); 7.86 (s, 1 H, CH=N). IR, ν/cm^{-1}: 1451, 1581, 1644 (C=N); 1735 (C=O); 2981.

***N*-Benzylidene-L-Ala *tert*-butyl ester (3c).** Yield 51%, b.p. 105—107 °C (1.5 Torr), n_D^{15} 1.5119, $[\alpha]_D^{20}$ −36° (c 1, $CHCl_3$). Found (%): C, 71.97; H, 8.27; N, 6.02. $C_{14}H_{19}NO_2$. Calculated (%): C, 72.07; H, 8.21; N, 6.00. ^{1}H NMR ($CDCl_3$), δ: 1.48 (s, 9 H, 3 Me); 1.50 (d, 3 H, Me, J = 6.3 Hz); 4.02 (q, 1 H, CH, J = 6.3 Hz); 7.34—7.86 (m, 5 H, Ph); 8.30 (s, 1 H, CH=N). IR, ν/cm^{-1}: 2979, 1735 (C=O); 1644 (C=N); 1451 (Ref. 28: IR, ν/cm^{-1}: 1740 (C=O); 1650 (C=N)).

***N*-4-Chlorobenzylidene-DL-Ala isopropyl ester (3d).** Yield 85%. ^{1}H NMR ($CDCl_3$), δ: 1.17, 1.21 (both d, both 3 H, 2 Me, both J = 6.0 Hz); 1.45 (d, 3 H, Me, J = 7.1 Hz); 4.95 (m, 1 H, OCH); 7.30—7.50 (m, 4 H, Ar); 8.26 (s, 1 H, CH=N). IR, ν/cm^{-1}: 1451, 1581, 1644 (C=N); 1735 (C=O); 2981.

***N*-2-Fluorobenzylidene-DL-Ala isopropyl ester (3e).** Yield 83%. ^{1}H NMR ($CDCl_3$), δ: 1.19, 1.23 (both d, both 3 H, 2 Me, both J = 6.1 Hz); 1.48 (d, 3 H, Me, J = 7.1 Hz); 5.05 (m, 1 H, OCH); 7.20—7.40 (m, 4 H, Ar); 8.59 (s, 1 H, CH=N).

***N*-Benzylidene-DL-Phe isopropyl ester (3f).** Yield 75%, b.p. 169—170 °C (2 Torr), n_D^{16} 1.5538. ^{1}H NMR ($CDCl_3$), δ: 1.23, 1.25 (both d, both 3 H, 2 Me, both J = 6.1 Hz); 3.25 (m, 2 H, CH_2); 4.15 (m, 1 H, CH); 5.07 (m, 1 H, OCH); 7.21—7.69 (m, 10 H, 2 Ph); 7.98 (s, 1 H, CH=N).

1-*O*-Benzyl-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-L-threitol (*O*-benzyl-(4*R*,5*R*)-TADDOL, 1b) was prepared by benzylation of compound **1a** with excess BnBr (3 equiv.) and

* Prepared by N. S. Ikonnikov (A. N. Nesmeyanov Institute of Organoelement Compounds of the RAS).

NaH (2.5 equiv.) in MeCN on refluxing of the reaction mixture and crystallized from a hexane—CH_2Cl_2 mixture, m.p. 224 °C, $[\alpha]_D^{20}$ −25.7° (*c* 1, $CHCl_3$). Found (%): C, 81.97; H, 6.45. $C_{38}H_{36}O_4$. Calculated (%): C, 81.98; H, 6.52. ^1H NMR ($CDCl_3$), δ: 0.76, 0.95 (both s, both 3 H, 2 Me); 3.60 (d, 1 H, CH, J = 10.0 Hz); 4.05 (AB system, 2 H, CH_2, $\Delta\nu$ = 20 Hz, J = 15.0 Hz); 4.30 (d, 1 H, CH, J = 10.0 Hz); 5.66 (s, 1 H, OH); 6.80—7.40 (m, 25 H, 5 Ph). IR, ν/cm^{-1}: 1019, 1034, 1042, 1057, 1082 (O—C—O); 3350 (Bn—O...H).

2,3-*O*-Isopropylidene-1,4-di-*O*-methyl-1,1,4,4-tetraphenyl-L-threitol (di-*O*-methyl-(4*R*,5*R*)-TADDOL, 1d) was synthesized by alkylation of compound **1a** with excess MeI (4 equiv.) in DMF in the presence of NaH (3 equiv.) at 50 °C, $[\alpha]_{578}^{25}$ −89.90° (*c* 1, $CHCl_3$). Found (%): C, 80.17; H, 7.02. $C_{33}H_{34}O_4$. Calculated (%): C, 80.12; H, 6.93. ^1H NMR ($CDCl_3$), δ: 0.86 (s, 6 H, 2 Me); 3.00 (s, 6 H, 2 Me); 4.88 (s, 2 H, 2 CH); 7.10—7.60 (m, 20 H, 4 Ph).

Alkylation of Schiff's bases 3a—f (typical procedure) (see Table 1, entry *4*). A solution of compound **1a** (0.047 g, 0.1 mmol) in 3 mL of anhydrous PhMe was placed in a dry flask filled with Ar (the reaction flask had been twice evacuated and heated in a flame of a burner followd by filling with Ar) and NaOH (0.16 g, 4 mmol) (powdered under Ar immediately prior to the experiment) was added. The suspension was stirred with a magnetic stirrer for 5 min, and a solution of Schiff's base **3b** (0.219 g, 1 mmol) (distilled *in vacuo* in an Ar flow) in 2 mL of dry PhMe and BnBr (0.14 mL, 1.2 mmol) were added successively in a flow of Ar. The mixture was stirred at room temperature (15—20 °C) for 12 h and 6 *N* HCl (6 mL) was added. The mixture was stirred for 1 h, the aqueous layer was separated, the organic layer was washed with 6 *N* HCl, and the aqueous solutions were combined. TADDOL was recovered by concentration of the organic layer and crystallization of the residue. The aqueous extract was refluxed for 5 h (to determine the chemical yield, an aliquot portion of a standard solution of Leu in 6 *N* HCl was added; the yield was found by integrating the signals of the Me groups in Leu and the CH_2 groups in Me-Phe in the ^1H NMR spectra), concentrated, and passed through a column with Dowex-50W resin (in the H^+ form); (*R*)-α-Me-Phe (0.145 g, yield 81%) was eluted with 5% ammonia, and the eluate was concentrated and analyzed by enantiomeric GLC (*ee* 82%). The amino acid was recrystallized from a Pr^iOH—H_2O mixture. Yield 40%, m.p. 288—290 °C (decomp.), $[\alpha]_D^{25}$ +17.8° (*c* 0.2, H_2O), *ee* >99% according to GLC (lit. for (*S*)-α-Me-Phe[23]: $[\alpha]_D^{25}$ −17.8° (*c* 0.2, H_2O), *ee* >99% according to GLC). Found (%): C, 67.12; H, 7.50; N, 7.87. $C_{10}H_{13}NO_2$. Calculated (%): C, 67.02; H, 7.31; N, 7.82. ^1H NMR ($CDCl_3$), δ: 1.31 (s, 3 H, Me); 2.90 (AB system, 2 H, CH_2, $\Delta\nu$ = 63 Hz, J = 14 Hz); 6.90—7.20 (m, 5 H, Ph). UV (H_2O), λ_{max}/nm (ε): 252 (139), 258 (178), 264 (135).

A similar procedure involving allyl bromide gave (*R*)-α-All-Ala; the use of α-naphthylmethyl chloride led to (*R*)-α-Me-Naphth-Ala; and the reaction with isopropyl iodide gave (*R*)-α-Me-Val. The enantiomeric purities of these products were also estimated by GLC based on a comparison with authentic samples.

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