Asymmetric PTC C-Alkylation Catalyzed by Chiral Derivatives of Tartaric Acid and Aminophenols. Synthesis of (*R*)- and (*S*)-α-Methyl Amino Acids

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A new type of efficient chiral catalyst has been elaborated for asymmetric C-alkylation of CH acids under PTC conditions. Sodium alkoxides formed from chiral derivatives of tartaric acid and aminophenols (TADDOL's **2a**−**e** and NOBIN's **3a**−**h**) can be used as chiral catalysts in the enantioselective alkylation, as exemplified by the reaction of Schiff's bases **1a**−**e** derived from alanine esters and benzaldehydes with active alkyl halides. Acid-catalyzed hydrolysis of the products formed in the reaction afforded (*R*)-α-methylphenylalanine, (*R*)-α-naphthylmethylalanine, and (*R*)-α-allylalanine in 61−93% yields and with ee 69−93%. The procedure could be successfully scaled up to 6 g of substrate **1b**. When (*S*,*S*)-TADDOL or (*R*)-NOBIN are used, the (*S*)-amino acids are formed. A mechanism rationalizing the observed features of the reaction has been suggested.

Introduction

Ion-pair-mediated reactions under phase-transfer conditions have been increasingly useful in organic synthesis since their introduction.[1] Until recently, there have been no successful applications of PTC conversions to catalytic asymmetric synthesis, except for a few cases, involving the use of cinchona alkaloid-derived quaternary ammonium salts, where however, the enantioselectivity is normally relatively low.[2] A significant improvement (ee higher than 90%) of the asymmetric alkylation of a glycine Schiff's base under PTC conditions using *N*-(9-anthracenylmethyl)-modified cinchonidinium salt as a catalyst and aqueous (aq) CsOH or aq KOH as a base has been reported by two independent groups.[3,4] Recently, O'Donnell introduced neutral, nonionic phosphazene bases,[5] and Maruoka reported new serC_2-symmetric chiral ammonium salts.[6] However, all the chiral catalysts of the quaternary ammonium type, with a possible exception in the last case, are efficient only at low temperatures.[2−5] The catalysts are also unstable in the presence of alkali decomposing to give achiral derivatives, whose competition with homochiral catalysts results in the formation of racemic products decreasing the enantioselectivity of the process.[2a] Chiral crown ethers were suggested by Cram as potent catalysts of asymmetric formation of C−C bonds.[7] Unfortunately, chiral crown ethers are expensive and their synthesis is tedious. Thus, the search for novel, active, stable, simple, and cheap chiral PTC-catalysts is still continuing.[8]

At the same time, asymmetric reactions of C−H acids carried out under the effects of chiral bases constitute an important class of organic transformations.[9] Asymmetric C-alkylations of achiral Li-enolates using chiral

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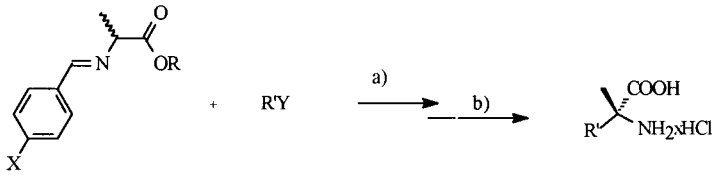
Scheme 1. Alkylation of Substrates 1 under PTC Conditions[a]



(*R,S*)-**1a**: R=Me, X=H

(*R,S*)-**1b**: R= ^{i}Pr, X=H

(*R,S*)-**1c**: R= ^{i}Pr, X=Cl

(*R,S*)-**1d**: R= ^{i}Pr, X=F

(*S*)-**1e**: R=^{t}Bu, X=H

α-Methyl-α-Amino Acids

c.y. 71-93%

e.e. 69-93%

R' = Bn, Allyl, α-Naphthylmethyl

Y = Br, Cl

ligands represents another important development.[9d] In all these cases, chiral ion pairs or chiral Li-organic compounds are formed and become the intermediates in the alkylation reactions of the carbanionic particles.

Recently, a pioneering work of L. Duhamel disclosed the first reported use of chiral alkoxides (derived from chiral β-amino alcohols) either as stoichiometric bases[9e] or basic catalysts[9f] to effect an asymmetric dehydrobromination reaction.

We supposed that another important class of organic reactions, C-alkylation of CH-acids with alkyl halides carried under PTC conditions, could be performed asymmetrically by use of dioles or other chiral hydrophobic, chelating agents − amino alcohols. We suggested that such dioles and amino alcohols would function in the reaction as chelating agents for the alkali ions and thus make the ion-pairs (formed by the corresponding carbanion and alkali ions) soluble in organic solvents. We believed that this modification could combine the synthetic simplicity of the PTC-approach[2−4] with the rigidity of the mutual orientations of the chiral ligand and the substrate in the transition state of the reaction, similar to the case of transition metal complex catalysis.[10,11]

This paper reports the results of the application of the PTC approach to the elaboration of asymmetric synthesis of α-methyl-α-amino acids (α-Me-AA), important synthetic targets.[12−14] For instance, α-allyl-α-alanine (α-All-Ala), α-methyl-α-naphthylalanine (α-Me-Napht-Ala) are valuable nonproteinogenic α-Me-AA.[2c−d,13,14] (*S*)-α-Methylphenylalanine (α-Me-Phe) is a very important compound for the synthesis of a new generation of solution stable aspartam derivatives.[12] Modern analysis of the pathways leading to α-Me-AA sets development of catalytic methods as a primary synthetic challenge.[12a]

In the present study, we propose a new class of phase transfer catalysts for the asymmetric PTC *C*-alkylation of Schiff's bases derived from esters of (±)-Ala (substrates **1**). The catalysts were either derivatives of tartaric acid (**2a**−**e**), such as easily available 1,4-chiral diol, (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol) (TADDOL, catalyst **2b**)[15−17] or 1,4-aminophenols, 2,2′-disubstituted binaphthyls (**3a**−**h**), such as (*S*)-2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, catalyst **3a**).[18] Preliminary results of this work were reported by us earlier.[19]

Results

Substrates **1** derived from benzaldehyde and racemic alanine esters Schiff's bases were suggested by O'Donnell as substrates for the synthesis of racemic amino acids with quaternary carbon atoms.[20] CH acidity of the substrates (pK_a ∼20, DMSO)[21] was sufficient for them to be alkylated in the presence of alkali hydroxides under PTC conditions.[2,20]

The alkylations of a substrate **1b** with benzyl bromide (BnBr) (see Scheme 1) were conducted in dry organic solvents at ambient temperature using solid NaOH (ground under argon) as base. Derivatives of tartaric acid, mostly TADDOL and its derivatives **2a**−**e**, 2,2′-dihy-

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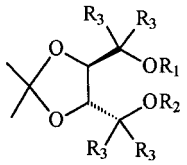
Chart 1



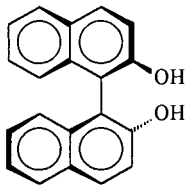
(*R*,*R*)-**2a**: R_1=R_2=R_3=H

(*R*,*R*)-,(*S*,*S*)-**2b**: R_1=R_2=H, R_3=Ph(TADDOL)

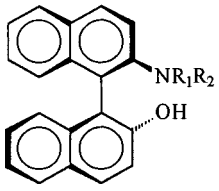
(*R*,*R*)-**2c**: R_1=Bn, R_2=H, R_3=Ph

(*R*,*R*)-**2d**: R_1=R_2=Me, R_3=Ph

(*R*,*R*)-**2e**: R_1=R_2=H, R_3=Naphtyl



(*R*)-BINOL



(*R*)- or (*S*)-**3a**: R_1=R_2=H (NOBIN)

(*S*)-**3b**: R_1=H, R_2=Me

(*S*)-**3c**: R_1=R_2=Me

(*R*)-**3d**: R_1=H, R_2= ^{i}Pr-

(*R*)-**3e**: R_1=H, R_2=C_6H_{11}

(*R*)-**3f**:R_1=H, R_2=Adamantyl

(*S*)-**3g**: R_1=H, R_2=Ph

(*R*)-**3h**:R_1=H, R_2=$(CH_2)_2OH$

Table 1. Asymmetric Synthesis of α-Me-Phe by C-Benzylation of Substrate 1b Promoted with Different Types of Catalysts under PTC Conditions[a]

run	catalyst	c.y. (%)	ee (%) (confign)
1	diethyl tartrate	0	0
2	(*R*)-BINOL	0	0
3	(*R*)-**2a**	40	15 (*R*)
4	(*R*)-**2b**,(*R*,*R*)-TADDOL	90	80 (*R*)
5	(*S*)-**2b**,(*S*,*S*)-TADDOL	80	82 (*S*)
6	(*R*)-**2c**	60	3 (*R*)
7	(*R*)-**2d**	58	3 (*R*)
8	(*R*)-**2e**	90	59 (*R*)
9	(*R*)-**3a**, (*R*)-NOBIN	90	60 (*S*)
10	(*S*)-**3a**, (*S*)-NOBIN	90	62 (*R*)

[a] The reaction conditions: toluene, ambient temperature, the concentration of the substrate was 0.2 M, the reaction was conducted for 15−24 h with the ratio of **1b**/BnBr/catalyst/NaOH = 1.0:1.2:0.1:4.0−5.0.

Table 2. Asymmetric Synthesis of α-Me-Phe by Benzylation of Compound 1b Mediated by NOBIN and Its Derivatives 3a-h[a]

run	catalyst **3a**−**h**	base	c.y.[b] (%)	ee (%) (confign)[c]
1	(*S*)-**3a**	NaOH	>90	62 (*R*)
2	(*S*)-**3a**	KOH	>90	43 (*R*)
3	(*S*)-**3b**	NaOH	>90	31 (*R*)
4	(*S*)-**3c**	NaOH	90	15 (*R*)
5	(*R*)-**3d**	NaOH	>90	8 (*S*)
6	(*R*)-**3e**	NaOH	>90	11 (*S*)
7	(*R*)-**3f**	NaOH	>90	10 (*S*)
8	(*S*)-**3g**	NaOH	>90	3 (*R*)
9	(*R*)-**3h**	NaOH	>90	17 (*S*)
10	(*S*)-**3a**	NaH	60	68 (*R*)[d]
11[e]	(*S*)-**3a**	NaH	80	22 (*S*)

[a] Concentration of the substrate was 0.4 M; the reactions were conducted at 20 °C over 12 h in toluene with a molar ratio of **1b**/BnBr/**3a**−**h**/NaOH (NaH) = 1.0:1.2:0.1:4.0 (1.0). [b] Determined by ^{1}H NMR, using leucine as an internal standard. [c] Chiral GLC analysis. [d] After crystallization, (*R*)-α-Me-Phe was obtained in 40% yield with >98% ee. [e] Substrate **4** (see Chart 2) was used.

droxy-1,1′-binaphthyl (BINOL) or 2-hydroxy-2′-amino-1,1′-binaphthyl (NOBIN) and its derivatives **3a**−**h** (Chart 1) were taken in catalytic amounts (10 mol %) as chiral promoters. After 12 h, the reaction product was decomposed under mild conditions to give α-Me-Phe hydrochloride which was analyzed, after derivatization by GLC on a chiral stationary phase (Table 1). Toluene was found to be the solvent of choice to get maximum ee of the final product.

We chose benzylation of Schiff's base formed from (±)-Ala and benzaldehyde as a model reaction for testing the efficiency of ligands (Table 1). Thus, BINOL and diethyl tartarate proved to be inefficient as both catalysts and asymmetry-inducing agents (see Table 1, runs 1 and 2). Another derivative of tartaric acid, (+)-2,3-*O*-isopropylidene-L-threitol, **2a**, was a more efficient promoter of the reaction with c.y. of α-Me-Phe as high as 40% and 15% ee (Table 1, run 3). (*S*,*S*)- and (*R*,*R*)-TADDOL, **2b** proved to be even more successful furnishing relatively high enantiomeric and chemical yields of α-Me-Phe (see Table 1, runs 4 and 5). In this case (*S*,*S*)-TADDOL gave (*S*)-α-Me-Phe. Mono and di-*O*-alkylation of TADDOL led to compounds **2c** and **2d** that retained some catalytic activity but failed to induce any asymmetry into the final product (Table 1, runs 6 and 7). (+)-2,3-*O*-Isopropylidene-1,1,4,4-tetra(2-naphthyl)-L-threitol, **2e**, likewise (*S*)- and (*R*)-NOBIN, **3a**, were catalytically active and capable of mediating moderate asymmetric induction into the final product of C-alkylation (Table 1, runs 9 and 10; (*S*)-NOBIN furnished (*R*)-α-Me-Phe.

The analysis of the catalytic activities of tartaric acid derivatives (Table 1, runs 1 and 3−8) testified that high hydrophobicity and the presence of free 1,4-hydroxyl groups were necessary features for the catalytic activity and asymmetric inducing power of this class of catalysts to be observed. Inactivity of BINOL might be traced to its higher OH acidity, as compared to TADDOL, and the formation of the insoluble disodium salt of the former under the reaction conditions, removing it from the reaction media. The asymmetric induction observed with NOBIN as a catalyst (Table 1, runs 9 and 10) showed that OH group could be substituted by a less acidic NH group and the asymmetric inducing power of the catalyst finally revealed.

The data summarized in Table 2 showed that the nature of base was important as the substitution of NaOH by KOH significantly decreased the ee of the

Table 3. Asymmetric Benzylation of Alanine Derivatives 1, Mediated by (*R*,*R*)-Taddol, (*R*)-2b[a]

run	substrate	catalyst (equiv)	base	(*R*)-α-Me-Phe, c.y.[b] (%)	(*R*)-α-Me-Phe, ee[c] (%)
1	**1a**	1.0	NaOH	0	0
2	**1a**	1.0	NaH	90	70
3[d]	**1e**	1.0	NaOH	90	22
4	**1b**	1.0	KOH	31	24
5	**1b**	1.0	LiOH	0	-
6	**1b**	1.0	$CsOHxH_2O$	94	0
7[e]	**1b**	1.0	NaOH	80	82
8[f]	**1b**	0.1	NaOH	92	80
9[g]	**1b**	0.1	NaOH	65	93
10	**1c**	0.1	NaOH	89	83
11	**1d**	0.1	NaOH	91	83
12[h]	**1b**	0.1	NaOH	54	77
13	**1b**	0.1	NaOH + 0.1 equiv of TMEDA	78	30
14	**1b**	0.1	NaOH + 0.1 equiv of Et_4NBr	83	0
15	**1b**	0.1	50% aq NaOH	79	0
16	**1b**	0.1	NaOH + 0.1 equiv of Na_2CO_3	65	21
17	**1b**	1.0	NaH	95	93
18	**1b**	0.1	NaH	90	40
19	**4**	1.0	NaH	85	10
20[i]	**1b**	1.0	NaH	90	70
21[j]	**1b**	1.0	NaH	20	71
22[k]	**1b**	1.0	NaH	40	93
23[l]	**1b**	1.0	NaH	70	87
24[m]	*m*	0.1	NaOH	80	4

[a] The concentration of the substrates in PhMe was 0.2 M; the reaction time was 12 h; $T = 15-20$ °C; the ratio of **1** or **4**/BnBr/**2**/NaOH (NaH) = 1.0:1.2:0.1−1.0:4.0−5.0 (2.0). [b] Determined by ^{1}H NMR, using leucine as an internal standard. [c] Chiral GLC analysis. [d] The initial alanine moiety was of (*S*)-configuration; the reaction time was 168 h. [e] (*S*,*S*)-TADDOL gave (*S*)-α-Me-Phe. After crystallization (*S*)-α-Me-Phe was recovered in 40% yield with ee greater than 99%.[19] [f] The reaction was conducted in hexane. [g] Using BnCl as an alkylating agent. [h] Scale-up experiment (see below). [i] 4 equiv of NaH was used. [j] 0.25 equiv of NaH was used. [k] 0.5 equiv of NaH was used. [l] 1 equiv of NaH was used. [m] A Schiff's base derived from benzaldehyde and racemic *i*-Pr ester of phenylalanine was alkylated with MeJ.

reaction (Table 2, runs 1 and 2). Any substitution of the NH bond by alkyl groups invariably decreased the asymmetric inducing power of NOBIN (Table 2, runs 1, 3−7, and 9). The effect was even more pronounced when a phenyl group was introduced into this position (Table 2, run 8). NaH was shown to be a superior base relative to NaOH (Table 2, run 10).

As our attempts on improving performance of the catalyst by modifications of NOBIN failed, further research efforts were concentrated on studying TADDOL, which showed greater synthetic potential (Table 1, compare run 4 with runs 8−10).

TADDOL, **2b**, at a ratio of 1/1 or 1/10 to the substrates effectively catalyzed asymmetric C-benzylation of all the substrates **1a**−**e** (see Table 3, runs 1−18, 20−23) with ee's ranging from 20% to 93% with NaOH or NaH used as bases. Surprisingly, the ee of the product did not fall below 40% in the case of NaH-promoted reaction even when the ratio of NaH/**2b** was decreased from 1/1 to 1/0.1 (Table 3, runs 17 and 18). (*R*,*R*)-**2b** furnished invariably (*R*)-α-Me-Phe, whereas (*S*,*S*)-**2b** gave (*S*)-α-Me-Phe (Table 3, run 7). TADDOL can be recovered from the reaction mixture and repeatedly used after crystallization without any loss of catalytic activity. A more hydrophobic derivative **2e** was much less efficient asymmetric catalyst with ee of only 59%, as compared to **2b** under the same experimental conditions (Table 1, runs 8 and 4).

Hexane was found to be a good medium for the reaction with chemical yields and asymmetric induction of the reaction being on the same level as those in toluene (Table 3, runs 8 and 12). Use of more polar solvents, such as CH_3CN, $CHCl_3$, and CH_2Cl_2 resulted in almost racemic product of the alkylation.

The leaving group in the alkylating agent seemed to influence the asymmetric induction in the reaction, as the switch from BnBr to BnCl improved the ee of the product from 80% to almost 93% (Table 3, runs 8 and 9) although the reaction became sluggish and the chemical yields dropped.

Any possible enrichment of the final alkylation product by a complex formation with **2b** during the product isolation was excluded by a control experiment where (*S*,*S*)-TADDOL and the racemic final product of the reaction (a Schiff's base of benzaldehyde and *i*-Pr ester of racemic α-methylphenylalanine) were mixed and treated in the conditions of workup, and no ee enrichment was found for the final α-methylphenylalanine.

The structure of the substrate was important to secure both high chemical yields of the product and its ee. The alkylation of **1a** in the presence of NaOH was not successful as the substrate was effectively hydrolyzed under the reaction conditions (Table 3, run 1) but use of NaH as a base was productive to give (*R*)-α-Me-Phe with 70% ee (Table 3, run 2). Naturally, *t*-Bu ester derivative, **1e**, was much more stable to the base catalyzed hydrolysis, but ee of the reaction was only 22% (Table 3, run 3). It seems that the introduction of different substituents into the aromatic moiety of the Schiff's base of alanine *i*-Pr ester had no effect on the ee of benzylation (Table 3, runs 10 and 11).

The type of base was vital, as there was no alkylation with LiOH (Table 3, run 5) and ee of the reaction dropped from 80 to 82% to 24% on substituting NaOH by KOH (Table 3, run 4 and 7). Similarly, no asymmetric induction was observed in the case of $CsOH \times H_2O$ (run 6) application. The addition of 50% of Na_2CO_3 to NaOH resulted in a diminished ee of the reaction (Table 3, run 16). Use of 50% aqueous NaOH led to complete disappearance of the asymmetric induction of **1b** benzylation (Table 3, run 15) and significant increase in the amount of the hydrolyzed product.

The addition of competitive PTC agents, such as Et_4NBr or chelating agents such as TMEDA to the reaction mixture either diminished or completely suppressed any asymmetric induction in the reaction (Table 3, runs 13 and 14).

TADDOL or NOBIN could be used to bring about the alkylation of **1b** with other active alkylating agents, as Table 4 (runs 1−5) illustrated. Aliphatic alkyl halides were either not active or asymmetric induction and chemical yields of the products were unsatisfactory (Table 4, run 6). Methylation of the Schiff's base formed from the isopropyl ester of D,L-Phe and benzaldehyde by MeI, catalyzed by TADDOL under the standard conditions resulted in a lower yield of (*R*)-α-Me-Phe with ee ∼4% (Table 3, run 24).

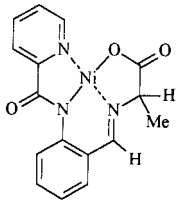
The CH acidity of the substrate (**4**, Chart 2**)** (pK_a ∼19, DMSO)[22] was also sufficient to enable the alkylation in the presence of alkali hydroxides under PTC condi-

Table 4. Asymmetric Alkylation of 1b According to Scheme 1 Mediated by TADDOL 2b or NOBIN 3a[a]

run	RX	catalyst (equiv)	catalyst	α-Me-AA, c.y.,[b] (%)	α-Me-AA, ee (%) (confign)[c]
1	allylBr	1.0	(*R*)-**2b**	91	73 (*R*)
2	allylBr	0.1	(*S*)-**2b**	89	70 (*S*)
3	allylBr	0.1	(*S*)-**3a**	90	67 (*R*)
4	1-naphthylCH$_2$Cl	0.1	(*R*)-**2b**	86	71 (*R*)
5	1-NaphthylCH$_2$Cl	0.1	(*S*)-**3a**	60	18 (*R*)
6	Pr^{i}Br	0.1	(*R*)-**2b**	25	12 (*R*)

[a] The concentration of the substrates in PhMe was 0.2 M; the reaction time was 12 h; T = 15−20 °C; the ratio of **1b**/BnBr/catalyst/NaOH = 1.0:1.2:0.1−1.0:4.0−5.0. [b] Determined by ^{1}H NMR, using leucine, as an internal standard. [c] Chiral GLC analysis.

Chart 2



(*R,S*)-**4**

tions.[23,24] Thus, TADDOL- and NOBIN-promoted asymmetric benzylation of substrate **4** (Table 2, run 11, and Table 3, run 19) but the asymmetric induction was low (10 and 24% ee, respectively).

Discussion

The products of alkylation of substrates **1** and **4** cannot undergo epimerization; therefore, the ratio of enantiomers obtained in the reactions reflected the actual kinetic stereoselectivity of the process.

It seems likely that NOBIN and its derivatives **3a**−**h** functioned in the reaction as bases, ionizing the substrate. The pK_a of **1e**, determined in DMSO, is in the range of 17−20,[21] whereas that of NOBIN is most likely about 18 (the measured pK_a value of phenol in DMSO is 18,[25] whereas the value for aniline is 30[26] (so as the value for tertiary aliphatic alcohols had been found close to 30 in the same solvent).[27] Hence, the catalyst is likely to be first ionized at its OH-group in an aprotic solvent in order to function as a base. On the other hand, the rigid structure of NOBIN could provide the necessary features to make it a hydrophobic complexing agent for cations. The transition state of the alkylation should involve both catalyst and alkali metal ion as revealed by the comparison of the solid NaOH and KOH (Table 2, runs 1 and 2). Thus, the chelating properties of the catalyst seemed to be indispensable with the NOBIN better fit for Na rather than K ions. Finally, an intermolecular hydrogen bond between the ionized substrate and −OH or/and −NH groups of the catalyst may stabilize the complex of the enolate ion pair with the catalyst, as the substitution at NH moiety invariably diminished ee of the reaction (Table 2, runs 3−9). In fact, the structure of the complex would be the same, regardless whether the sodium salt of NOBIN served initially as a hydrophobic base or the neutral catalyst functioned as a chelating agent in the same manner as disclosed for another chiral catalyst of Li-enolate alkylations.[9c,d] In our case, the unreactive aggregates of the sodium enolates[28] generated from **1** may be activated for the C-alkylation by the complexation with catalyst.

It was more difficult to ascribe the same kind of mechanism to TADDOL as pK_a of tertiary alcohols had been found to be close to 30 in the same solvent[27] where pK_a of class **1** substrates was determined.

The absence or presence of minute amounts of the products of O-alkylation of TADDOL in the reaction mixture, despite the presence of its alcoholate in the solution, can be attributed to the steric hindrance preventing the alkylation reaction. The difficulty of TADDOL alkylation was confirmed by the blank experiment; even prolonged refluxing of TADDOL with excess of NaOH and BnBr in MeCN resulted only in formation of α-monoalkylated derivative of TADDOL, i.e., **2c**. Very low asymmetric induction observed for the **2c**-catalyzed reaction proved that it is TADDOL and not its O-alkylated products (that might eventually be formed in the reaction media), which is the real catalyst of the reaction.

To elucidate the mechanism, a series of experiments was carried out differing from our standard procedure[19] as the order of addition of the components was concerned. TADDOL and NaOH in toluene were placed in a dry flask filled with argon and stirred for several hours. Then, the resulting heterogeneous mixture was filtered in a flow of argon to remove the excess of solid alkali. Substrate **1b** and BnBr were added successively in a flow of argon to the homogeneous filtrate, which could contain only TADDOL and/or the alcoholate of TADDOL. After stirring and the standard workup, (*R*)-α-Me-Phe was isolated in a 33% yield and ee 79%. This meant that it was alcoholate of TADDOL (contained in the filtrate), which actually catalyzed enantioselective alkylation of the substrate. Thus, under the experimental conditions, the alkali metal alcoholates of TADDOL functioned as chiral hydrophobic bases soluble in toluene in the same way as NOBIN. Similarly, the rigid structure of TADDOL was favorable for the chelate formation with the sodium ions and much less complementary for Li, K, and Cs ions (Table 3, runs 4−6). Finally, an intramolecular hydrogen bond between the ionized substrate and TADDOL can stabilize the complex formed by the enolate, alkali ion and TADDOL, as any substitution of its OH groups by OR drastically decreased ee of the reaction (see Table 1, runs 4−7). Water and any chelating competitors natu-

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Table 5. The Dependence of the Enantiomeric Purity of the Product of 1b Benzylation [*(R)*-α-Me-Phe] on the Enantiomeric Purity of Catalyzing *(R,R)*-Taddol[a]

run	ee of *(R)*-α-MePhe	ee of *(R,R)*-TADDOL
1	42	50
2	42	61
3	85	80
4	80	82

[a] The reaction conditions and methods of analysis are the same as in the reference to Table 3.

rally ruined the asymmetry inducing performance of the catalyst (Table 3, runs 13−15).

It is difficult to estimate if it was one or two OH groups of TADDOL that were ionized under the experimental conditions without any kinetic experiments, and if it was mono- or bis-alcoholate which constituted the real catalyst. Still there is a broad maximum of the asymmetric induction of the reaction centered at a 1:1 NaH/TADDOL ratio. Also the analogy with NOBIN could support a notion that the mono-alcoholate of TADDOL functioned as the real catalytic particle in the PTC C-alkylation reaction.

Finally, the question of the number of TADDOL molecules in the catalytic complex has to be addressed. A very rough linear correlation between the ee of TADDOL and that of the product (α-Me-Phe) of **1b** benzylation was observed (see Table 5, runs 1−4), indicating that most likely only one molecule of TADDOL was present in the catalytic complex (for a discussion of nonlinear effects, see ref 29).

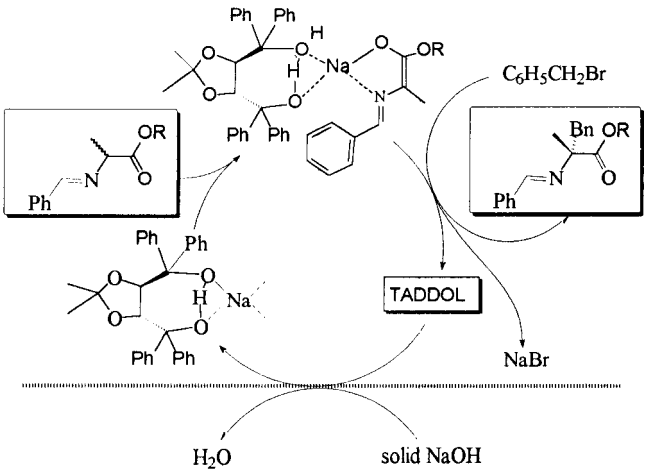
As data collected in Table 2 (run 11) and Table 3 (run 19) indicated, substrate **4** was invariably inferior substrate relative to **1b** (Table 2, runs 10 and 11; Table 3, runs 20 and 19) or even **1a** (Table 3, run 2) in terms of asymmetric induction under the identical conditions. Obviously, the carbanion of **4** was functioning as a monodentate ligand with too many degrees of freedom of rotation in the chiral ion pair. The obvious reason for the better performance of the substrates **1a**−**d**, as compared to **4**, lies in the ability of their carbanion to chelate sodium ions in a mixed chiral complex with TADDOL (see Scheme 2). Compound **1e** proved to be a slowly reacting substrate, giving low ee of the final product (Table 3, run 3). In this case the sterically demanding substrate preventing formation of the complex between the enolate ion pair and TADDOL together with spontaneous alkylation of the hydrophobic (and thus more soluble in toluene) sodium salt of **1e** might be the underlying reason for this obvious deviation.

The highly hypophetical mechanism of the catalytic action of TADDOL or NOBIN is depicted in Scheme 2, as applied to the TADDOL case. At the surface of solid NaOH, TADDOL becomes ionized, the alcoholate thus formed acts as a chiral base in an organic solvent, ionising **1b**. The chiral ion pair, consisting of the substrate enolate and TADDOL complexed with the metal ion, is the intermediate species that undergoes alkylation. After the complex had been alkylated, TADDOL (or NOBIN) is released to participate in a new catalytic cycle.

Conclusions

In summary, we propose a new type of efficient chiral catalysts for asymmetric *C*-alkylation of CH acids under

Scheme 2. Possible Mechanism of TADDOL-Mediated Asymmetric PTC Alkylation of 1



PTC conditions. The conditions for the alkylation were not optimized and higher ee of the alkylation could be expected when lower temperatures, improved catalysts, etc. were employed. The procedure could be successfully scaled up to 6 g of substrate **1b** (see the Experimental Section). Our results compare favorably with other methods of asymmetric PTC alkylations, employing chiral derivatives of alkaloids,[2−5] in terms of the catalyst stability and recovery, and the ambient temperature of the reaction. Thus, new asymmetric alkylations of various C−H acids can be envisaged, using our approach with chelates tailor-made for each particular application. We believe that further increase in the number of chelating catalysts would allow the enantioselectivity of this reaction to be increased.

Experimental Section

General Methods. The IR-spectra were taken in KBr plates. All chemical shifts are reported as δ values (ppm) relative to C_6D_6 as an external standard. The optical rotations were measured at 25 ± 0.2 °C in $CHCl_3$ unless otherwise stated. The electronic absorption spectra were carried out with matched pair of quarts cells. Melting points are uncorrected. The reactions were monitored by TLC on Silufol plates; for TLC silicagel 60 F254 (Merck) was employed. Enantiomeric GLC analyses[30] of (a) α-Me-Phe, (b) α-All-Ala, and (c) α-Me-Napht-Ala were performed on a Chirasil-L-Val type phase, by using *n*-propyl esters of *N*-trifluoroacetyl derivatives of amino acids. Fused silica capillary column 40m × 0.23 mm i.d. Phase film thickness 0.12 μm. Column temperature: (a) 125 °C, (b) 75 °C, (c) 160 °C. Carrier-gas He: 1.80 bar.

All reactions were performed under a dry argon atmosphere. Hexane and toluene were distilled over Na prior to the reaction (the water content was ≤0.01%; determined by the Fischer method). Granules of NaOH (Reakhim or Merck) were powdered in a glovebox filled with Ar immediately prior to the reaction. For preparation of aminonaphthols **3a**−**g** see ref 18. Compound **3h** was prepared by reaction of **3a** with ethylene oxide.[31] Commercial diols **2a** (Merck) and (−)-2,3-*O*-isopropylidene-1,1,4,4-tetra(2-naphthyl)-L-threitol (**2e**) (Fluka) were used. ^{t}Butyl ester of L-alanine was received from Aldrich. All the synthesized compounds had the appropriate physical and chemical data.

(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-bis(diphenylmethanol) [(*R*,*R*)-TADDOL (2b)] were synthesized by previ-

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ously described procedures:[15,16] mp 196−198 °C; $[\alpha]^{20}_D$ −61.5° (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 6H, 2Me); 4.01 (s, 2H, 2CH); 7.30−7.50 (m, 20H, 4Ph) (lit.[15] mp 193−195 °C; $[\alpha]^{20}_D$ −66.7 (*c* 1, $CHCl_3$)). **(4*S*,5*S*)-TADDOL (*S*,*S*)-2b)** was synthesized by analogy.

1-*O*-Benzyl-2,3-isopropylidene-1,1,4,4-tetraphenyl-L-treitol (2c) was prepared by benzylation of compound **2b** with excess BnBr (3 equiv) and NaH (2.5 equiv) in MeCN on refluxing of the reaction mixture during 18h (see ref 15 and 16) and crystallized from hexane/CH_2Cl_2: mp 224 °C; $[\alpha]^{20}_D$ −25.7 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.76, 0.95 (both s, both 3H, 2Me), 3.60 (d, 1H, CH, J = 10.0 Hz), 4.05 (AB system, 2H, CH_2, $\Delta\nu$ = 20 Hz, J = 15.0 Hz), 4.30 (d, 1H, CH, J = 10.0 Hz), 5.66 (s, 1H, OH), 6.80−7.40 (m, 25H, 5Ph); IR (KBr) 1019, 1034, 1042, 1057, 1082 (O−C−O), 3350 (Bn-O···H) cm^{-1}. Anal. Calcd for $C_{38}H_{36}O_4$: C, 81.98; H, 6.52. Found: C, 81.97; H 6.45.

2,3-Isopropylidene-1,4-di-*O*-methyl-1,1,4,4-tetraphenyl-L-treitol (2d) was synthesized by alkylation of compound **2b** with excess MeI (4 equiv) in DMF in the presence of NaH (3 equiv) at 50 °C during 24 h: $[\alpha]^{20}_{578}$ −89.90 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (s, 6H, 2Me), 3.00 (s, 6H, 2Me), 4.88 (s, 2H, 2CH), 7.10−7.60 (m, 20 H, 4 Ph). Anal. Calcd for $C_{33}H_{34}O_4$: C, 80.12; H 6.93. Found: C, 80.17; H 7.02.

Ni(II) complex of the Schiff base of D,L-Ala and *N*-(2-pyrridylcarbonyl)-*o*-aminobenzaldehyde (4) was prepared by a previously described procedure:[23] mp 286 °C dec (lit.[23] mp 286°C dec). Anal. Calcd for $C_{16}H_{13}N_3NiO_3$: C, 54.29; H, 3.70;, N, 11.87. Found: C, 53.83; H, 3.57; N, 11.85.

Schiff's bases **1a**−**f** were synthesized by standard procedures[32] from benzaldehydes and the corresponding Ala ester.

***N*-Benzylidene-D,L-alanine methyl ester (1a):** yield 66%; colorless oil; bp 112−113 °C (2.5 Torr) (lit.[32] mp 105−107 °C (2 Torr)); n^D_{15} 1.5378; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (d, 3H, Me, J = 7.0 Hz), 3.29 (s, 3H, OMe), 3.80 (q, 1H, CH, J = 7.0 Hz), 6.60−7.30 (m, 5H, Ph), 7.86 (s, 1H, CH=N); IR (KBr) 1451, 1581, 1643 (C=N), 1742 (C=O), 2952 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 68.30; H, 6.85, N 7.32. Found: C, 68.30; H, 6.82, N 8.19.

***N*-Benzylidene-D,L-alanine isopropyl ester (1b):** yield 71%; bp 120−121 °C (2 Torr); n^D_{15} 1.5168; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23, 1.27 (both d, both 3H, 2Me, J = 6.2 Hz), 1.51 (d, 3H, Me, J = 7.1 Hz), 3.80 (m, 1H, OCH), 3.29 (q, 1H, CH, J = 7.1 Hz), 6.60−7.30 (m, 5H, Ph), 7.86 (s, 1H, CH=N); IR (KBr) 1451, 1581, 1644 (C=N), 1735 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.18; H, 7.82; N, 6.55.

***N*-4-Chlorobenzylidene-D,L-alanine isopropyl ester (1c):** yield 85%; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17, 1.21 (both d, both 3H, 2Me, both J = 6.0 Hz), 1.45 (d, 3H, Me, J = 7.1 Hz), 4.00 (q, 1H, CH, J = 7.1 Hz), 4.95 (m, 1H, OCH), 7.30−7.50 (m, 4H, Ar), 8.26 (s, 1H, CH=N); IR (KBr) 1451, 1581, 1644 (C=N), 1735 (C=O) cm^{-1}.

***N*-4-Fluorobenzylidene-D,L-alanine isopropyl ester (1d):** yield 83%; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19, 1.23 (both d, both 3H, 2Me, J = 6.1 Hz), 1.48 (d, 3H, Me, J = 7.1 Hz), 4.10 (q, 1H, CH, J = 7.1 Hz), 5.05 (m, 1H, OCH), 7.20−7.40 (m, 4H, Ar), 8.59 (s, 1H, CH=N).

***N*-Benzylidene-L-alanine *tert*-butyl ester (1e):** yield 51%; colorless oil; bp 105−107 °C (1.5 Torr); n^D_{15} 1.5119; $[\alpha]^{20}_D$ −36° (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9H, 3Me), 1.50 (d, 3H, Me, J = 6.3 Hz), 4.02 (q, 1H, CH, J = 6.3 Hz), 7.34−7.86 (m, 5H, Ph), 8.30 (s, 1H, CH=N), IR (KBr) 2979, 1735 (C=O), 1644 (C=N) 1451 cm^{-1} (lit.[33] IR (KBr) 1740 (C=O), 1650 (C=N) cm^{-1}). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.97; H, 8.27; N, 6.02.

***N*-Benzylidene-D,L-phenylalanine isopropyl ester (1f):** yield 75%; bp 169−170 °C (2 Torr); n^D_{16} 1.5538; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23, 1.25 (both d, both 3H, 2Me, both J = 6.1 Hz), 3.25 (m, 2H, CH_2), 4.15 (m, 1H, CH), 5.07 (m, 1H, OCH), 7.21−7.69 (m, 10H, 2Ph), 7.98 (s, 1H, CH=N).

Alkylation of Schiff's Bases 1a−f (Typical Procedure). A solution of compound **2b** (0.047 g, 0.1 mmol) or **3a** (0.0285 g, 0.1 mmol) in 3 mL of anhydrous PhMe was placed in a dry flask containing a stirring bar and filled with Ar (the reaction flask had been twice evacuated and heated in a flame of a burner followed by filling with Ar). NaOH (0.16 g, 4 mmol) (powdered under Ar immediately prior to the experiment) or NaH (oil covered) was added, and the suspension was stirred for 5 min. Then, a solution of the Schiff's base **1** (0.219 g, 1 mmol) (distilled in vacuo in an Ar flow) in 2 mL of dry PhMe and benzyl bromide (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 stirring was continued for an additional 15 min at the ambient temperature, the aqueous layer was separated, the organic layer was washed with 6 N HCl, and the aqueous layers were combined. Catalyst was recovered by concentration of the organic layer and crystallization of the residue. The aqueous extract was refluxed for 1 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 GLC for enantiomeric composition (ee 82%). The crude amino acid thus produced could be recrystallized from an *i*-PrOH−H_2O mixture to give the enantiomerically pure (*R*)-α-Me-Phe: yield 40%; mp 288−290 °C dec; $[\alpha]^{25}_D$ +17.8 (*c* 0.2, H_2O), ee >99% according to GLC (lit.[34] for (*S*)-α-Me-Phe $[\alpha]^{25}_D$ −17.8 (*c* 0.2, H_2O), ee >99% according to GLC); ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (s, 3H, Me); 2.90 (AB system, 2H, CH_2, J = 14.0 Hz), 6.90−7.20 (m, 5H, Ph); UV λ_{max}/nm (ϵ) 252 (139), 258 (178), 264 (135). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H 7.31; N, 7.82. Found: C, 67.12; H 7.50; N, 7.87.

A similar procedure involving allyl bromide gave (*R*)-α-allylalanine ((*R*)-α-All-Ala); the use α-naphthylmethyl chloride led to (*R*)-α-(1-naphthylmethyl)alanine ((*R*)-α-Me-Napht-Ala, and the reaction with isopropyliodide gave (*R*)-α-Me-Val. The enantiomeric purities of these products were also estimated by GLC based on a comparison with authentic samples of the amino acids.[34]

Alkylation of 4 with Benzyl Bromide. The alkylation was performed as described for the alkylation of Schiff's bases **1a**−**f** (see above). The recovery and enantiomeric analysis of α-Me-Phe was carried out as described in ref 23.

Alkylation of Schiff's Bases 1b with Benzyl Bromide (Scale-Up Procedure). A solution of (*S*,*S*)-TADDOL **2b** (1.34 g, 2.88 mmol) in 110 mL of anhydrous hexane was placed in a dry flask, containing a stirring bar, and Ar (see above) and NaOH (4.6 g, 115 mmol) (powdered under Ar immediately prior to the experiment) were added and the suspension was stirred for 15 min. Then, a solution of the Schiff's base **1b** (6.3 g, 28.8 mmol) (distilled in vacuo in an Ar flow) in 10 mL of dry hexane and benzyl bromide (0.14 mL, 1.2 mmol) were added successively in a flow of Ar. The mixture was stirred at 20 °C for 20 h, and hexane was evaporated. Then benzene (100 mL) and 6 N HCl (100 mL) were added. The stirring was continued for an additional 15 min, the aqueous layer was separated, the organic layer was washed with 6 N HCl, and the aqueous layers were combined. The catalyst was recovered from organic layer. The aqueous extracts were refluxed for 6 h and evaporated, a fresh portion of 2 N HCl was added, and the solution was passed through a column with DOWEX-50W resin (in the H^+ form). (*R*)-α-Me-Phe (2,8 g, 15.6 mmol, yield 54.3%) was eluted with 5% ammonia, and the eluate was concentrated and analyzed by enantiomeric GLC (ee 77.3%). The crude amino acid thus produced was recrystallized from

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an Pr^iOH-H_2O mixture to give (*R*)-α-Me-Phe (1.8 g, yield 34.8%, ee 98.1%).

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