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Asymmetric PTC *C*-alkylation mediated by TADDOL — novel route to enantiomerically enriched α-alkyl-α-amino acids †

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Abstract

Compound (4*R*,5*R*)- or (4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) was shown to catalyze *C*-alkylation of aldimine Schiff's bases of alanine esters under phase-transfer catalysis conditions (solid NaOH, toluene, ambient temperature, 10% TADDOL) with the e.e. of the final α-methylphenylalanine or α-allylalanine reaching 82%.

1. Introduction

Asymmetric reactions of C–H acids carried out under the influence of chiral bases constitute an important class of organic transformations.[1a] Use of chiral ligands for the purpose of asymmetric catalysis of the *C*-alkylation reaction of achiral Li–enolates represents another important development.[1b] Recently, pioneering work of L. Duhamel disclosed the first reported use of chiral alkoxides (derived from chiral β-amino alcohols) either as stoichiometric bases[2a] or basic catalysts[2b] to effect an asymmetric dehydrobromination reaction. We have found that a mixture of NaH and (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL,[3] see Fig. 1) served as a chiral base to induce

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† Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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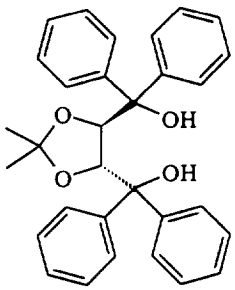
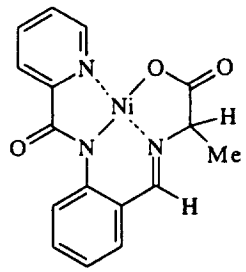


(*R*,*R*)-TADDOL



rac-**1**

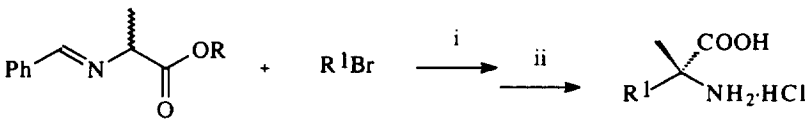
Fig. 1.

asymmetry in a Michael addition reaction of an achiral glycine derivative, resulting in enantiomerically enriched (28% e.e.) γ-substituted glutamic acid.[4]

We supposed that another important class of organic reactions, *C*-alkylation of C–H acids with alkyl halides, could be carried out asymmetrically by use of TADDOL. This paper reports the results of the application of the idea to the asymmetric synthesis of α-methyl substituted α-amino acids which represent an important class of nonproteinogenic amino acids.[5]

2. Results and discussion

For this purpose four C–H acids were chosen: a Ni(II) complex of the racemic alanine Schiff's base, **1** (see Fig. 1); the Schiff's base derivatives of benzaldehyde and racemic alanine methyl ester, **2a**; isopropyl ester, **2b**; and (*S*)-alanine t-butyl ester, **2c**. The alkylations of the substrates with benzyl bromide or allyl bromide were conducted in toluene (carefully dried before use) at the ambient temperature (15–20°C) using NaH or solid NaOH (ground under Ar) as bases and TADDOL (either stoichiometric or catalytic amounts) as a chiral promoter (see Scheme 1, illustrating the alkylation of class-**2** substrates). The experimental results were summarized in Table 1.



rac-**2a**: R= Me
rac-**2b**: R= *i*-Pr
(*S*)-**2c**: R= *t*-Bu

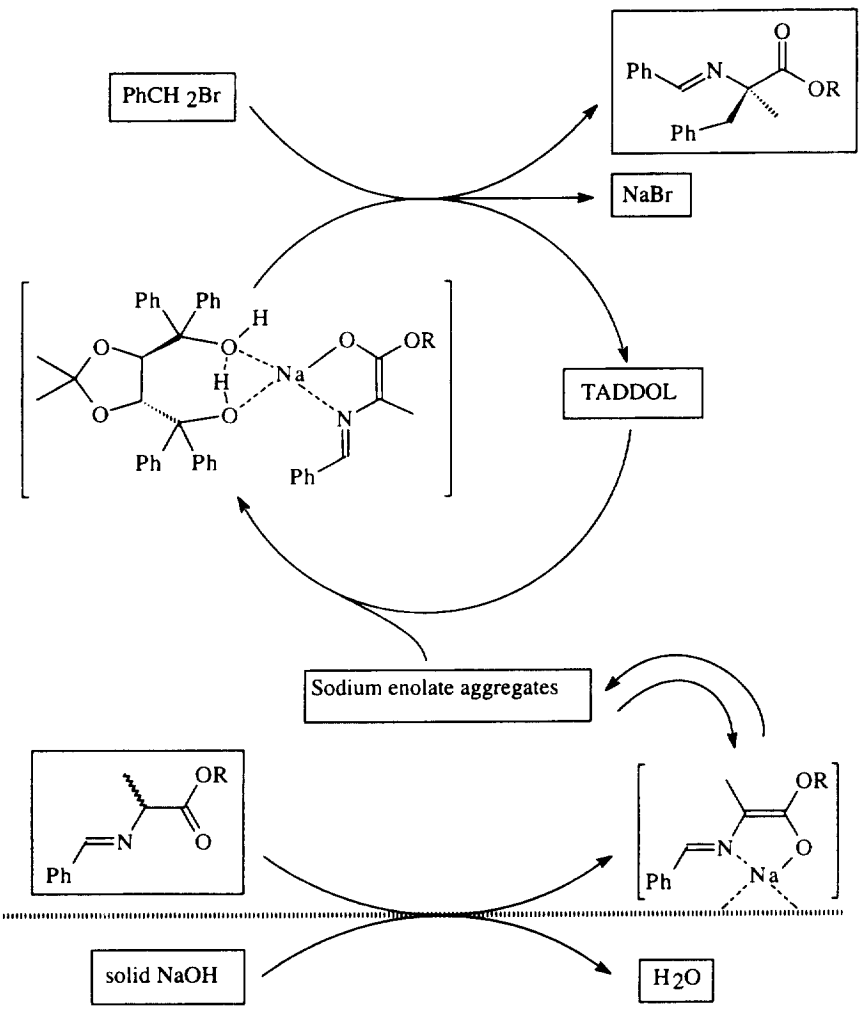
R¹ = benzyl; allyl

e.e. up to 82% (*R*)

Scheme 1. Reagents and conditions: (i) solid NaOH (4–5 eq.) or NaH (2–4 eq.), (*R*,*R*)-TADDOL (0.1 –1.0 eq.), toluene, Ar, r.t., 15–24 h; (ii) 6 N HCl (aq.), r.t., 1 h, extraction of TADDOL, reflux, 5 h

The alkylation of **2** with ethyl bromide under the experimental conditions proceeded very slowly.

As can be seen from the data, both (*R*,*R*)- and (*S*,*S*)-TADDOL were efficient asymmetric promoters of the alkylation reactions (e.e. in the range of 20–82%) with both types of bases and active alkylation agents (see Table 1, runs 1–9, 11–14, 16, 17). (*R*,*R*)-TADDOL furnished (*R*)-α-methylphenylalanine or (*R*)-α-allylalanine (runs 1–11, 14, 16 and 17) whereas (*S*,*S*)-TADDOL gave (*S*)-α-methylphenylalanine (run 12).



Scheme 2. Possible mechanism of TADDOL mediated asymmetric PTC alkylation of **2a–c**

catalyst[10] and e.e. of the final products.[9,11] TADDOL and its derivatives are readily available[3] and can be readily modified.[12] Thus a host of new asymmetric alkylations of different C–H acids can be envisaged, using our approach, with different TADDOL modifications tailored for each particular application.

3. Experimental section

Synthesis of **1** and **2a–c** were performed as described earlier (see Belokon' et al.[13] and Grigg et al.[14] respectively). Synthesis of *O*-monobenzyl TADDOL was performed by benzylation of TADDOL with benzyl bromide in the presence of sodium hydride in MeCN. All the synthesized compounds had the appropriate physical and chemical data. GLC enantiomeric analyses of (a) α-methylphenylalanine and (b) α-allylalanine were performed on a Chirasil-L-Val type phase, by using their *N*-trifluoroacetyl *n*-

propyl esters. Fused silica capiliary column 40 m×0.23 mm ID. Film 0.12 mkm. Col. temp.: (a) 125°C, (b) 75°C. Carrier-gas He: 1.80 bar.

The alkylation of the substrates **2** were carried out as follows. A 25 mL flask containing a stirring bar was flame dried *in vacuo* and filled with Ar. (*R,R*)-TADDOL (0.047 g, 0.1 mmol), NaOH (0.20 g, 5 mmol, ground under Ar before use) (or NaH, oil covered), a solution of the Schiff's base **2b** (0.219 g, 1 mmol, distilled *in vacuo* under Ar) in dry toluene (5 mL, distilled over Na before use) and benzyl bromide (0.14 mL, 1.2 mmol) [or allyl bromide (0.11 mL, 1.2 mmol)] were added to the flask. The mixture was stirred at room temperature (15–20°C) for 15–24 h and aq. HCl (6 N, 6 mL) was added. The stirring was continued for 1 h at ambient temperature, then the aqueous layer was separated, the toluene layer washed with 6 N aq. HCl and the washings and the aqueous layer were combined. TADDOL could be recovered from the toluene layer after its evaporation *in vacuo*, followed by crystallization. The aqueous solution (a standard solution of (*S*)-Leu in 6 N HCl could be added to it if c.y. had to be established) was refluxed for 5 h. (*R*)-α-Methylphenylalanine (the yield could be established by the ^{1}H NMR) was purified by the ion-exchange technique (DOWEX-50, H^+ form) and its e.e. determined by GLC. Crude amino acid was recrystallized from ^{i}PrOH–H_2O, $[\alpha]_D^{25}$ +17.8 (c 0.2, H_2O), e.e.>99% by GLC; (the data for the sample of (*S*)-α-methylphenylalanine specially obtained by an earlier developed method[15]: $[\alpha]_D^{25}$ −17.8 (c 0.2, H_2O)). The procedure could be successfully scaled up to 10 g of **2**.

Acknowledgements

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Table 1
The asymmetric alkylation of different alanine derivatives mediated by (*R,R*)-TADDOL in toluene at 15–20°C [a]

runs	Substrate	R	Base	TADDOL (equiv)	c.y.% [b]	e.e. (*R*)-aa [c]
1	**1**	-	NaH	1.0	85	20
2	**2a**	Me	NaH	1.0	90	70 [d]
3 [e]	**2a**	Me	NaH	1.0	92	70
4	**2à**	Me	NaH	0.1	95	43
5	**2b**	*i*-Pr	NaH	1.0	84	60
6	**2b**	*i*-Pr	NaH	0.1	80	30
7 [f]	**2b**	*i*-Pr	NaH	1.0	91	75
8 [f]	**2b**	*i*-Pr	NaH	0.1	96	40
9 [g]	**2c**	*t*-Bu	NaH	1.0	81	40
10	**2a**	Me	NaOH	1.0	0	-
11	**2b**	*i*-Pr	NaOH	1.0	80	82
12	**2b**	*i*-Pr	NaOH	0.1	81	82 [i,j]
13 [h]	**2b**	*i*-Pr	NaOH	1.0	68	3
14	**2b**	*i*-Pr	KOH	1.0	31	24
15	**2b**	*i*-Pr	LiOH	1.0	0	-
16 [g]	**2c**	*t*-Bu	NaOH	1.0	45	38
17 [g]	**2c**	*t*-Bu	NaOH	0.1	93	22

[a] The concentration of the substrates was 0.2 M unless indicated otherwise; the reactions were conducted for 15-24 h with a ratio of alanine derivatives **1** or **2** : R'Br : TADDOL : NaOH (NaH) = 1.0 : 1.2 : 0.1–1.0 : 4.0–5.0 (2.0–4.0); the alkylating agent was BnBr, unless indicated otherwise; the substrates were racemic unless indicated otherwise. [b] Determined by ^{1}H NMR, using leucine as an internal standard. [c] See experimental section for details of chiral GLC analysis on crude products. [d] The average of three experiments. [e] The concentrations of the reagents were increased fivefold (1 M). [f] The alkylating agent was allyl bromide. [g] The alanine moiety was of (*S*) configuration; the reaction was continued for 168 h. [h] The promoter was *O*-monobenzyl TADDOL. [i] After crystallization it was recovered in 40% yield with greater than 99% e.e. [j] (*S,S*)-TADDOL gave (*S*)-α-methylphenylalanine with the same e.e.

Any possible enrichment of the final alkylation product by TADDOL during the product isolation was excluded by a control experiment where TADDOL and the final racemic product were mixed and treated in the conditions of the work up and no e.e. were found for the final α-methylphenylalanine.

O-Monobenzyl derivative of TADDOL was also a promoter of the reaction but the asymmetric induction was very low (Table 1, run 13).

We believe it unlikely that under the experimental conditions TADDOL functions as a base. The pK_a of the substrates **1** and class **2**, as determined in DMSO, (see Terekhova et al.[6a] and O'Donnell et al.[6b] respectively), were in the range of 17–20 whereas the pK_a of tertiary alcohols had been found close to 30 in the same solvent.[7] Thus it seems improbable that TADDOL was the first to be ionized in an aprotic solvent in order to function as a base. Besides, TADDOL recovered from the reaction mixture was intact (it could be reused after a crystallization) and no products of its *O*-alkylation were detected after the reaction. These observations argue indirectly against any significant ionization of TADDOL under the experimental conditions. On the other hand, the rigid structure of TADDOL could provide the necessary features to make it a hydrophobic complexing agent of cations in the manner indicated by Scheme 2. In fact, experiments proved that TADDOL was able to extract some sodium picrate (solid) to toluene. Finally, an intermolecular hydrogen bond between the ionized substrate and TADDOL might stabilize the complex between the enolate ion pair and TADDOL. In fact, the structure of the complex would be the same whether TADDOL sodium salt served initially as a hydrophobic base or the neutral TADDOL functioned in the same manner as disclosed for another chiral catalyst of Li–enolate alkylations.[1b] In our case the unreactive racemic aggregates of the sodium enolates generated from **1** or **2**[8] might be activated for the *C*-alkylation by the complexation with TADDOL (Scheme 2).

The e.e. of the reaction product depended strongly on the structure of the substrate. The lowest e.e was observed for the alkylation of **1** with benzyl bromide (20% e.e., Table 1, run 1). The substrates of type-**2** gave invariably better chemical yields and enantiomeric purities (see Table 1, runs 2–6, 11, 12, 16 and 17). The alkylation of **2a**, using NaOH as a base, was the only exception (Table 1, run 10) due to methyl ester group hydrolysis of the substrate, efficiently removing it from the reaction media. The obvious reason for the better performance of the substrates **2a–c**, as compared to **1**, lies in the ability of their carbanions to chelate sodium ions in a mixed chiral complex with TADDOL (see Scheme 2), providing a rigid structure where the *Si*-side of the carbanions was effectively shielded from the electrophilic attack (the mixed complex might have a much more complicated structure with other molecules of TADDOL and the substrate or its enolate taking part). Obviously, the carbanion of **1** was functioning as a monodentate ligand with too many degrees of rotation freedom in the chiral ion pair.

The type of base was important, as the e.e.s of the alkylations decreased from e.e 60–70% to 43–30%, going from the stoichiometric catalysis by TADDOL (runs 2, 3 and 5) to catalytic quantities (runs 4 and 6) if the base was NaH. No such decrease was observed if the base was NaOH (runs 11 and 12). Even the e.e. of the alkylation of **2b** increased in those cases from 30–60% (runs 5 and 6) to 82% (runs 10 and 11). The cation of the base was also important. For example, LiOH was completely inactive (Table 1, run 15) whereas the use of KOH furnished the product with a disappointingly low e.e. 24% (Table 1, run 14). The structure of the class **2** substrates also influenced the e.e of the alkylation, as an increase in the size of the ester group from Me to i-Pr was accompanied by the decrease of the alkylation e.e. from 70% to 60% (Table 1, compare runs 2 and 3 with 5). Compound **2c** proved to be a slow reacting substrate, giving low e.e. of the final product (Table 1, run 9). In this case the steric difficulty of the complex formation between the enolate ion pair and TADDOL and the competing spontaneous alkylation of the hydrophobic, and more soluble in toluene, sodium salt of **2c** might be the underlying reason for this obvious deviation.

The enantiomeric purity of (*R*)-α-methyl-α-phenylalanine could be greatly increased by crystallization (Table 1, run 12), as already disclosed.[9]

In summary, our results offer a novel approach to the creation of new generations of efficient chiral catalysts of asymmetric *C*-alkylation of C–H acids, including PTC conditions. The conditions of the alkylation were not optimized and higher e.e.s of the alkylations could be expected under lower temperatures and change of TADDOL structure, etc. Our results compare favorably with other methods of asymmetric PTC alkylations, employing chiral derivatives of alkaloids[9,10] in terms of both stability of the

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