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Enantioselective synthesis of (*S*)-α-methylphenylalanine using (*S*)-BINOLAMs as new phase-transfer catalysts

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Abstract—A series of (*S*)-bis(aminomethyl)binaphthols [(*S*)-BINOLAMs] **4** have been prepared and used as catalysts in the enantioselective *C*-alkylation reaction of the aldimine Schiff bases of alanine esters **5** under solid–liquid phase-transfer catalysis (PTC) conditions employing NaOH as base in toluene at room temperature. (*S*)-3,3′-Bis[(diethylamino)methyl]-2,2′-dihydroxy-1,1′-binaphthalene **4a** gave the best e.e.s. (*S*)-α-Methylphenylalanine **7** was isolated, after hydrolysis of the iminoester, in 85% yield with an e.e. of 68%.

Phase-transfer catalysis (PTC) is an effective tool for accelerating and controlling the regiochemistry and stereochemistry of many synthetic processes.[1] Asymmetric PTC has been successfully implemented in the synthesis of α-amino acids in an enantiomerically pure form,[2] thereby giving an alternative approach to alkylation of chiral templates.[2a,3] This methodology is also attractive because the procedure is scaleable and can be performed very simply and easily. A number of chiral salts, acting as PTC agents, have been employed for this purpose. The chiral cinchona alkaloid-derived ammonium salts are widely used,[4] O'Donnell's pioneering work[5] being the first enantioselective synthesis of amino acids using PTC conditions. Independently, the work of Lygo et al.[6] and Corey et al.[7] improved e.e.s previously obtained by O'Donnell et al. using modified cinchonine and cinchonidine catalysts, respectively. In conjunction, chiral ammonium salts and the phosphazene bases BEMP or BTPP also afforded α-amino acids in good e.e.[8] Polymer-supported cinchona alkaloids have also shown interesting catalytic activity in the asymmetric synthesis of α-amino acids and they can be easily recovered in an enantiomerically pure form and re-used without appreciable loss of activity.[9] Rigid chiral spiro ammonium salts with a binaphthyl structure[10] and phosphonium salts[11] have also been found to be effective catalysts.

Based on the pioneering experiments of Duhamel[12] where chiral alkoxides were employed as bases in stoichiometric and substoichiometric amounts, (*S*,*S*)- or (*R*,*R*)-TADDOL **1**,[13,14] (*R*)- or (*S*)-NOBIN **2**[13a,15] and its derivatives have been applied in the enantioselective alkylation of Schiff bases of alanine and glycine esters. The reaction performed with NOBIN is particularly interesting because the chiral catalyst could be recovered after an extractive work-up. In addition, chiral salen–metal complexes have been employed as PTC agents in the enantioselective alkylation of iminoalaninates, obtaining the best e.e. using Cu(II) salts.[16]

We prepared new NOBIN related aminoalcohols, namely enantiomerically pure (*S*)-3,3′-bis(aminomethyl)-2,2′-dihydroxy-1,1′-binaphthalenes (BINOLAMs) **4**, and examined their application as PTC agents in substoichiometric amounts in the enantioselective *C*-alkylation reaction of the alanine-derived iminoester **5**. This enantioselective reaction with benzyl bromide alkylating agent drove to α-methylphenylalanine (*S*)-**7** [α(Me)Phe] after acidic hydrolysis. α-Methylphenylalanine **7** belongs to a family of non-proteinogenic α-methyl-α-amino acids (AMAAs) which have interesting utilities and applications in many scientific areas.[2a,3] The α-(Me)Phe has been incorporated in sweeteners as a substitute for L-Phe, whilst the α-(Me)Phe analogue of aspartame has the same

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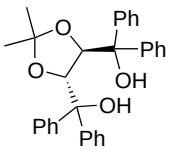
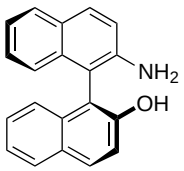
sweetness but higher stability than the unsubstituted analogue.[17] The AMAA substitution pattern also favours β-turn and helix formation when included in peptide sequences.[3d]



1 (*R*,*R*)-TADDOL



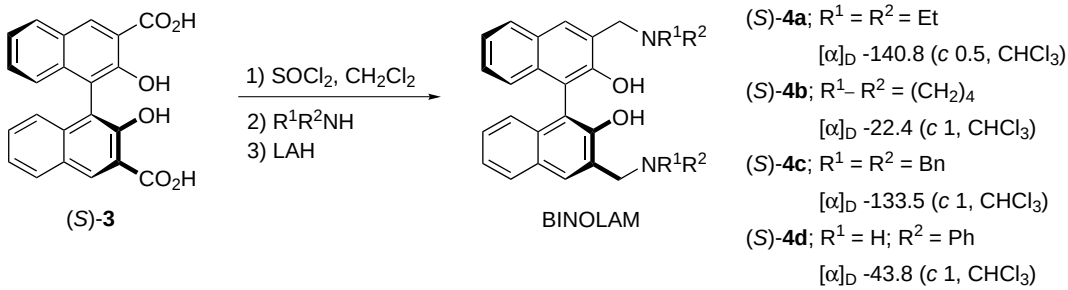
2 (*S*)-NOBIN

(*S*)-BINOLAMs **4** were prepared according to Scheme 1. Diacid **3**, prepared from methyl 3-hydroxy-2-naphthalenecarboxylate,[18] was resolved using L-leucine methyl ester hydrochloride following a known procedure.[19] The (*S*)-**3** enantiomer was treated with thionyl chloride affording the corresponding dichloride, which was immediately treated with diethylamine, pyrrolidine, dibenzylamine or aniline. The final reduction of the carbonyl group was accomplished with lithium aluminium hydride (LAH) affording ligands (*S*)-**4a**, (*S*)-**4b**, (*S*)-**4c** and (*S*)-**4d** in good yield (53–58% from diacid **3**) (Scheme 1).

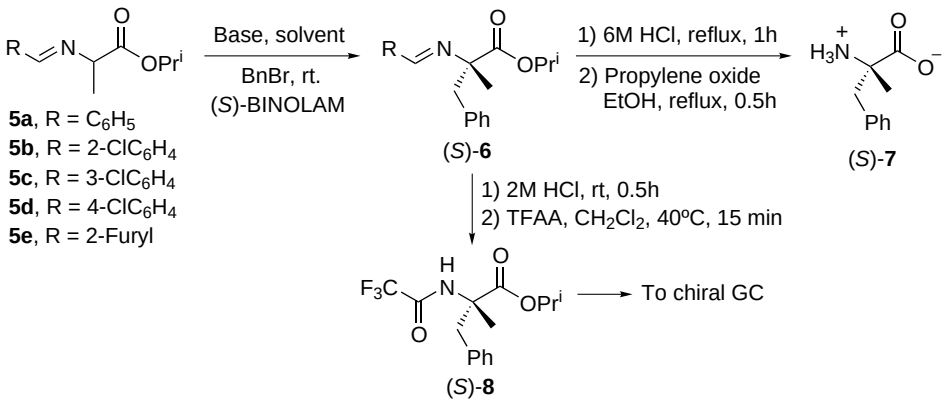
Chiral ligands **4** were used as solid–liquid phase-transfer catalysts in the *C*-alkylation reaction of alanine-derived *iso*-propyl iminoesters **5** with benzyl bromide as electrophile, affording compounds (*S*)-**6** in high yields (Scheme 2 and Table 1). These iminoesters, derived from aldehydes, are the appropriate substrates for the quaternisation of alanine esters.[2] In addition, the *iso*-propyl ester group is easily obtained and offers the same hydrolytic resistance to inorganic bases as the corresponding *tert*-butyl derivative.[6–13]

We initially employed (*S*)-BINOLAM **4a** in screening the reaction parameters for the asymmetric *C*-alkylation reaction with benzyl bromide (1 equiv.), using toluene in the presence of three equivalents of base (Table 1, entries 1–8). Sodium hydride gave a 40% e.e. of (*S*)-**9a** at room temperature (entry 1). The same reaction completed at 0°C lead to an increase in the e.e. of the product to 50% at the expense of longer reaction time. Unfortunately the alkylation reaction did not take place at the lower temperatures (–20 and –40°C, entry 2) examined in this study. Inorganic bases afforded very different and puzzling results. Thus, while solid sodium hydroxide furnished product with moderately good enantioselectivity (57% e.e.), caesium and potassium hydroxides induced lower enantioselection (entries 3, 6 and 7).

It is worth remarking that in this reaction (*S*)-BINOLAM **4a** was recovered in more than 80% yield after washing the free (*S*)-**7** amino acid with THF at the end of the synthesis. Lithium *tert*-butoxide was found to be unsuitable as a base for this asymmetric transformation as illustrated in entry 8. Next, we tested the best base (solid NaOH) in the presence of several solvents (entries 9–12) but the e.e. of compound **6a** was not improved. Only the reaction performed with xylene afforded a comparable diastereoselection (entry 10, 53% e.e.) to that found in toluene. *n*-Hexane, mesitylene and THF



Scheme 1.



Scheme 2.

Table 1. Enantioselective *C*-alkylation reaction of iminoesters **5** mediated by chiral aminoalcohols **4a–d**[a]

Entry	**4** (mol%)	**5**	Solvent	Base	Time (h)	(*S*)-**6**		(*S*)-**7**	
						Yield (%)[b]	E.e. (%)[c]	Yield (%)[d]	E.e. (%)[e]
1	**4a** (5)	**5a**	Toluene	NaH	44	**6a** >95	40	85	46
2	**4a** (5)	**5a**	Toluene	NaH[f]	55	**6a** >95	50	85	59
3	**4a** (5)	**5a**	Toluene	NaOH	40	**6a** >95	57	83	68
4	**4a** (100)	**5a**	Toluene	NaOH	10	**6a** >95	41	86	48
5	**4a** (100)[g]	**5a**	Toluene	NaOH	>48	**6a** <11	–	–	–
6	**4a** (5)	**5a**	Toluene	KOH	48	**6a** >95	<5	–	–
7	**4a** (5)	**5a**	Toluene	$CsOH·H_2O$	46	**6a** >95	21	–	–
8	**4a** (5)	**5a**	Toluene	$LiOBu^t$	22	**6a** >95	<5	–	–
9	**4a** (5)	**5a**	*n*-Hexane	NaOH	5	**6a** >95	<5	–	–
10	**4a** (5)	**5a**	Xylene	NaOH	17	**6a** >95	53	82	61
11	**4a** (5)	**5a**	Mesitylene	NaOH	18	**6a** >95	<5	–	–
12	**4a** (5)	**5a**	THF	NaOH	1	**6a** >95	<5	–	–
13	**4a** (5)	**5a**	Toluene	NaH[h]	40	**6a** >95	23	–	–
14	**4b** (5)	**5a**	Toluene	NaOH	23	**6b** >95	<5	–	–
15	**4c** (5)	**5a**	Toluene	NaOH	21	**6c** >95	33	81	38
16	**4d** (5)	**5a**	Toluene	NaOH	45	**6d** >95	8	–	–
17	**4a** (5)	**5b**	Toluene	NaOH	18	**6a** >95	51	84	59
18	**4a** (5)	**5c**	Toluene	NaOH	28	**6a** >95	20	–	–
19	**4a** (5)	**5d**	Toluene	NaOH	48	**6a** 88	35	88	40
20	**4a** (5)	**5e**	Toluene	NaOH	16	**6a** >95	<5	–	–

[a] The concentration of the substrate **5** was 0.12 M, employing 3 equiv. of base at room temperature.
[b] Determined by ^{1}H NMR.
[c] Obtained from the e.e. of the corresponding amidoesters **8** determined by chiral GC (Chirasil Val).
[d] After crystallisation of the free amino acid (*S*)-**7**.
[e] Determined by comparison with the optical rotation of pure (*S*)-**7**.
[f] Reaction run at 0°C.
[g] NaOH (1 equiv.) and (*S*)-BINOLAM (1 equiv.) were used.
[h] ZnI_2 (3 equiv.) was added to the reaction mixture.

gave very disappointing results (entries 9, 11 and 12). In order to increase the enantiomeric purity of (*S*)-**7** we studied the behaviour of chiral ligands **4b**, **4c** and **4d** (entries 14, 15 and 16). In spite of the structural similarity of chiral ligands, (*S*)-BINOLAM **4a** was found to be the most efficient catalyst for this process. Attempted transmetalation by adding stoichiometric amounts of additives such as CuI[13a,15] and ZnI_2 in the reactions using NaH as base led to disappointing results. Thus, copper iodide inhibited the *C*-alkylation reaction whereas zinc iodide afforded product with a 23% e.e. (entry 13). The possible role of the aryl substituents of the imine moiety was briefly examined. Several cases were studied (entries 17–20), the most significant result being that obtained with the *o*-chlorobenzaldehyde imine **5b** (entry 17, 51% e.e.).

Enantiomeric excesses were determined by chiral GC (Chirasil Val) analysing the *N*-trifluoroacetyl derivatives (*S*)-**8**[20] (Scheme 2). In addition e.e.s of iminoesters **6** were also roughly estimated by ^{1}H NMR employing (*R*)-*O*-aryllactic acids (ROAL)[21] as chiral solvating agents and found to be in agreement with chiral GC determinations. The (*S*)-enantiomer **6** was always generated as the major enantiomer whatever (*S*)-catalyst employed. Its absolute configuration was confirmed by the specific optical rotation value of the pure free (*S*)-α-methylphenylalanine **7** {$[\alpha]_D^{25} = 22.1$ (*c* 1, H_2O) for the pure (*S*)-enantiomer},[22] isolated in 81–88% yield after hydrolysis of **6** in refluxing 6 M HCl for 1 h and further treatment with propylene oxide in refluxing ethanol. The obtained α-methylphenylalanine **7**, after crystallisation from ethanol, was of higher enantiomeric purity than its precursor **6**, as reported.[13a,15]

As a possible mechanism of BINOLAM-mediated asymmetric PTC *C*-alkylation reaction of iminoesters **5** we assume that the mechanism previously suggested for NOBIN applies.[13a,15] Chelation of the chiral bisaminobinaphthol to the sodium atom of the enolate of **5** is considered key to the chiral induction observed. Similarly, for BINOL and BINOLAM aminoalcohols, the sodium enolates are the most suitable and reach the highest enantioselection. According to the results obtained from entries 4 and 5 we can suggest that the (*S*)-BINOLAM monosodium salt is not an active catalytic species because it has a more rigid structure and less coordination sites than the (*S*)-BINOLAM **4a** disodium salt, which is generated using a large excess of NaOH (300 mol%) and chiral ligand (5 mol%).

In summary, the new ligand (*S*)-3,3′-bis[(diethylamino)methyl]-2,2′-dihydroxy-1,1′-binaphthalene (*S*)-(BINOLAM) **4a**, easily prepared using known methodology, can be applied to the enantioselective *C*-alkylation reaction of iminoesters derived from alanine. (*S*)-BINOLAM **4a** can be recovered in high yield after extractive work up without any loss of optical

activity, which makes this methodology economic and scaleable. Further investigations into the applications of (*S*)-BINOLAMs as chiral catalysts in this and several other enantioselective reactions are currently in progress.

Acknowledgements

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