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Chiral quaternary benzophenone hydrazonium salt derivatives; Efficient chiral catalysts for the enantioselective phase-transfer alkylation of imines. Application to synthesis of chiral primary amines.

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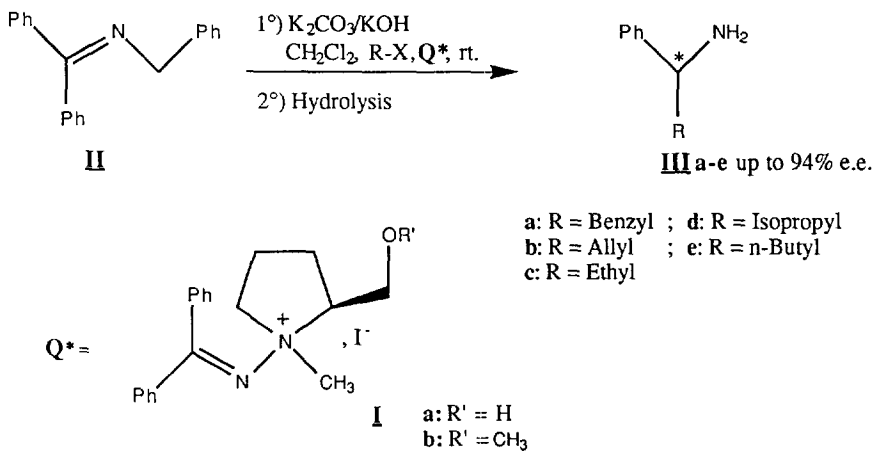
Abstract: (2S)-1-Methyl-1-[N-(diphenylmethylene)]-2-hydroxymethylpyrrolidine hydrazonium iodide **I-a** has been designed to catalyse the enantioselective phase-transfer alkylation of N-(diphenylmethylene) benzenemethanamine **II**. Although the weak acidic character of the latter, alkylations have been performed within reasonable reaction times. Optically active primary amines **III a-e** have been prepared in good chemical yields and up to 94% e.e. using 2-5 mol-% of the chiral catalyst only.

Non stoichiometric enantioselective conversion of organic molecules is considered as a big challenge as the recent literature reveals considerable interest in the subject[1]. Few examples of chiral auxiliaries, modified to be used as phase-transfer catalysts, are known to perform good enantiodifferentiation in alkylation reactions. A survey of the enantioselective phase -transfer alkylation literature shows that optically active β-aminoalcohol ammonium salts, have been effective in ketone[2] and Schiff base[3] catalytic asymmetric alkylation and chiral Michael addition[4] among other reactions. They also give moderate to good optical yields when used as ligands under catalytic conditions other than phase-transfer[5].

We report in this paper the design and use of (2S)-1-methyl-1-[N-(diphenylmethylene)]-2-hydroxymethylpyrrolidine hydrazonium iodide **I-a**, a new specifically designed chiral catalyst, in the alkylation of the aromatic imine **II** under solid-liquid phase-transfer conditions leading to optically active primary amines (Eq.1).



II

III a-e up to 94% e.e.

a: R = Benzyl ; **d**: R = Isopropyl
b: R = Allyl ; **e**: R = n-Butyl
c: R = Ethyl

Q* =

I **a**: R' = H
b: R' = CH_3

Eq. 1

Our interest in compound **II** has been based on a good knowledge of structurally similar substrates as we have been involved in mechanistical investigations of the enantioselective alkylation of enolates derived from α-aminoester Schiff bases[6]. Furthermore, it's a readily prepared[7] and good precursor for the synthesis of chiral primary amines if one considers their biological importance[8] as well as the limited number of reactions described[9].

For the design of the chiral catalyst, we first studied the low energy conformations[10] of substrate **II** together with some of it's deprotonated derivatives. In the light of this study, structures of the catalyst having the same imine moiety as **II** were chosen thinking of possible π–π interactions[11] and eventually a prefered molecular overlapping in the ion pair between the catalyst and the substrate. However, computer simulated chiral aggregates as model transition states, revealed that these moieties can never engage face-to-face arrangement because of the non coplanarity of the imine phenyl groups. Nevertheless, we noticed that such interaction is sterically possible exclusively between the conjugated phenyl group of the catalyst, which is coplanar with the imine double bond, and the benzyl part of the substrate. Thus, with a minimized structure in which a chiral β-aminoalcohol ammonium salt was linked to the first suggested moiety of the catalyst, stacked conformers showed one favoured face available sterically. Moreover,in the overlapped conformers the best ion-pairing, in terms of proximity between the prochiral center of the substrate and the quaternary nitrogen as well as the hydroxy group of the catalyst, was observed when the ionic nitrogen was directly bonded to the sp^2 nitrogen of the imine part suggesting a chiral hydrazonium salt derivative[12]. We therefore kept the same Schiff base part as in substrate **II** that we bonded to (S)(-)-prolinol[13] as the chiral β-aminoalcohol. A single stereogenic center was prefered for a better understanding of the stereochemical outcome of the alkylation.

Table 1. Enantioselective phase-transfer alkylation of imine **II** catalysed by **I-a**.

Entry	R-X	mol-% of **I-a**	Reaction time (h)	Amine **III**				e.e.[c] (%)
					yield[a] (%)	$[\alpha]_D$[b],	(conc)	
1	Benzyl-Br	2	24	**a.**	70	-10.1	(1.96)	91
2	Allyl-Br	2	19	**b.**	65	-28.8	(1.04)	90
3	Ethyl-Br	2	22	**c.**	75	-33.3	(1.00)	91
4	i-Propyl-Br	2	18	**d.**	75	-10.6	(1.00)	92
5	n-Butyl-Br	2	20	**e.**	70	-11.4	(1.00)	90
6	Benzyl-Br	5	24	**a.**	70	-10.45	(1.88)	94

[a] Yields are based on isolated amines[14]. [b] All $[\alpha]_D$ values were taken in chloroform as solvent.[c] Determined by polarimetry based on the maximum values described[9,15]. The major enantiomers have (S) configuration. Optical yields were not optimized.

From these data it appears that 2 mol-% of the designed chiral catalyst were sufficient to obtain high chemical and optical yields which have been in the ranges of 70 and 90% respectively. When 5 mol-% of the catalyst were used, the e.e. value increased to 94% (entry 6 vs. entry 1) and remained constant above this proportion.

The reaction times were as high as predicted having in mind the relatively high pka value of substrate **II**[16]. Surprisingly, alkylation with isopropyl bromide needed less time (compare entries 1, 3 and 4) although it is the most sterically hindred alkylating agent in our study. The proportion of the catalyst, however, did not seem to affect the reaction time (entry 6).
In spite of the low acidity of imine **II**, deprotonation rate of the less activated methylene group was accelerated by the high lipophilicity of the chiral catalyst and the efficiency of the base system used[17]. It has to be noted that no alkylation was observed with classical ammonium salts after 48 hours under the same reaction conditions. Compound **I-a** should be a good catalyst candidate for the phase-transfer alkylation of imines for which the reaction is limited by the pka barrier[18].

Finally, if we assume that the reacting species interact as their stable conformations, and if we consider π-stacking as the interaction responsible for the observed selectivity[11b], the molecular modeling study predicted (S) configuration for the chiral amines as observed. Indeed, in the transition state discussed earlier, molecular multifit corresponding to the best ion pairing showed clearly that the alkylating agent can only attack from the (si) face which is the only one available sterically. Furthermore, additional possible ionic interaction between the hydroxy group of the stereogenic center[19] of the catalyst and the substrate anion, must provide even better ion pairing. We have confirmed this hypothesis experimentally by synthesizing amine **III-c** using catalyst **I-b** in which attraction via hydrogen bonding was eliminated. Comparable chemical yield was obtained within the same reaction time (entry 3) but the optical yield decreased considerably [58% (**I-b**) vs. 91% (**I-a**)]. However, more evidence is needed to confirm the validity of the proposed transition state.

Attention is focused currently on optimization of the optical yields by studying the influence of the different reaction parameters. Improvement and recovery of the chiral catalyst, together with generalization of the reaction to the synthesis of other optically active organic molecules, will be the subject of future investigations.

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alkylated imine was purified by column chromatography (silica gel, hexane/diethyl ether: 95/5). The pure alkylated imine was taken in diethyl ether (5ml), aqueous HCl (10%) (5ml) was added and the mixture was stirred at room temperature till complete hydrolysis. The aqueous layer was washed with diethyl ether (3x15ml) and evaporated *in vacuo* to yield the amine hydrochloride salt. Pure free amines were obtained as described in reference 9. All their spectral data were in agreement with assigned structure.

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