Pergamon

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Tetrahedron Letters 44 (2003) 5629–5632

TETRAHEDRON LETTERS

Identification of a highly effective asymmetric phase-transfer catalyst derived from α-methylnaphthylamine

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Received 9 May 2003; accepted 30 May 2003

Abstract—A library of quaternary ammonium salts has been generated via reaction of simple chiral amines with a series of conformationally dynamic biphenyl units. Screening of this library against the alkylation of a glycine imine has led to the identification of a highly effective asymmetric phase-transfer catalyst derived from α-methylnaphthylamine.
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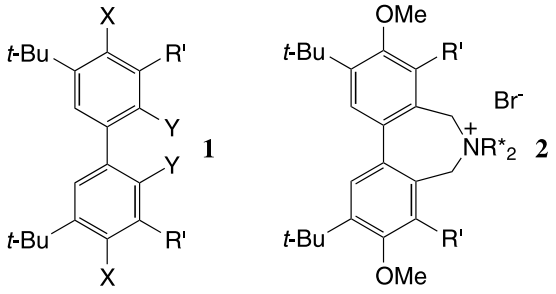
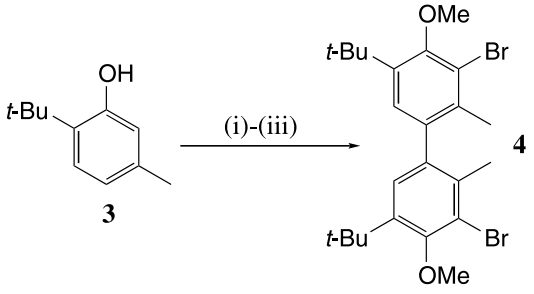
Induced atropisomerism is increasingly being recognised as a useful strategy for amplifying the effect of simple chiral elements in asymmetric catalysis. In particular, the replacement of atropisomerically stable binaphthyl components with their conformationally dynamic biphenyl analogues has received significant attention in recent years.[1] Biphenyls offer the advantage that they are generally less expensive to prepare (no resolution required) and allow for a wider variety of substitution around the initial aryl ring. In addition, their conformationally dynamic nature means there are no matched/mismatched issues when they are incorporated into structures containing other chiral elements.



Recently it has been shown that a binaphthyl-derived C_2-symmetric quaternary ammonium salt incorporating a conformationally flexible biphenyl group can act as a highly effective catalyst for the asymmetric alkylation of glycine imines.[2] Within this context we have become interested in the potential utility of biphenyls of type **1** (X = C or O, Y = C or O). We envisaged that compounds of this type would be straightforward to prepare from inexpensive commercially-available materials, and that variation of the substituents X, Y and R′ would allow for large libraries of structures to be generated. In this paper we describe preliminary results of a study in which we examined if it would be possible to generate effective asymmetric phase-transfer catalysts **2** via combination of biphenyls **1** with simple commercially-available chiral secondary amines.

The biphenyl core utilised in this study was conveniently prepared as outlined in Scheme 1. Thus *o*-bromination of commercially-available phenol **3**,[3] followed by oxidative coupling[4] and *O*-methylation gave the key dibromide **4** in good overall yield.

We have recently developed a simple automated approach for the generation and screening of quaternary ammonium salt libraries, and demonstrated that this can be applied to the optimisation of cinchona



Scheme 1. *Reagents and conditions*: (i) NBS, CCl_4, rt (60%); (ii) CuCl, TMEDA, MeOH, rt (88%); (iii) K_2CO_3, MeI, DMF, rt (98%).

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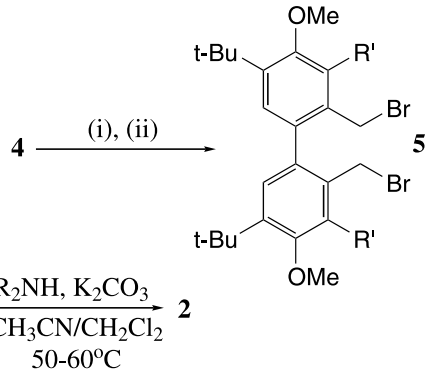
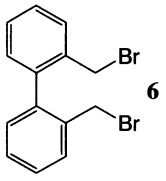
doi:10.1016/S0040-4039(03)01352-2

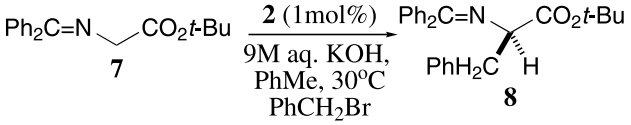


Scheme 2. *Reagents and conditions*: (i) R′-B(OH)$_2$, Pd(PPh$_3$)$_4$, K$_2$CO$_3$, THF, 70°C; (ii) NBS, *hv*, AIBN, CCl$_4$.



alkaloid derived catalysts.[5] Applying a similar approach here we next generated a library of quaternary ammonium salts **2** from compound **4** via (where appropriate) Suzuki coupling followed by radical bromination[6] and salt formation (Scheme 2). For comparison a series of quaternary ammonium salts derived from the unsubstituted bis-bromomethylbiphenyl unit **6** were also prepared.

In total 40 quaternary ammonium salts were generated in this study and these were then tested on the alkylation of glycine imine **7** (Scheme 3).



Scheme 3.

The enantioselectivities observed ranged from −30 to 91% e.e.[7] (Fig. 1), with the majority of salts tested favouring formation of the (*R*)-isomer of **8**. From these results a number of general observations can be made. Firstly, this study did indeed result in the identification of catalysts that were capable of high levels of asymmetric induction. Moreover, it appears that C_2-symmetrical systems are not necessarily required. Indeed in this study the most effective catalysts found were those derived from the simplest chiral amines; (*R*)-α-methylbenzylamine and (*R*)-α-methylnaphthylamine. Secondly, it appears that both the chiral amine and the conformationally flexible biphenyl unit play important roles in determining the overall selectivity of the alkylation process. All the salts derived from biphenyl **6** gave low levels of induction (−2 to 6% e.e.), suggesting that, at least for the amines investigated here, further substitution in the biphenyl unit is essential. It also appears that the substituent R′ has a significant influence on the stereoselectivity.[8] For example, the salt generated from (*R*)-*N*-methyl-α-methyl naphthylamine and biphenyl **5a** (R′ = Br) gave similar but *opposite* levels of enantioselectivity compared with the salt generated from the same amine and biphenyl **5b** (R′ = Ph).

The most effective catalyst identified in this study was **9**, and in order to further probe its potential as an asymmetric phase-transfer catalyst we briefly examined the effect of catalyst loading, base and reaction temperature (Table 1).

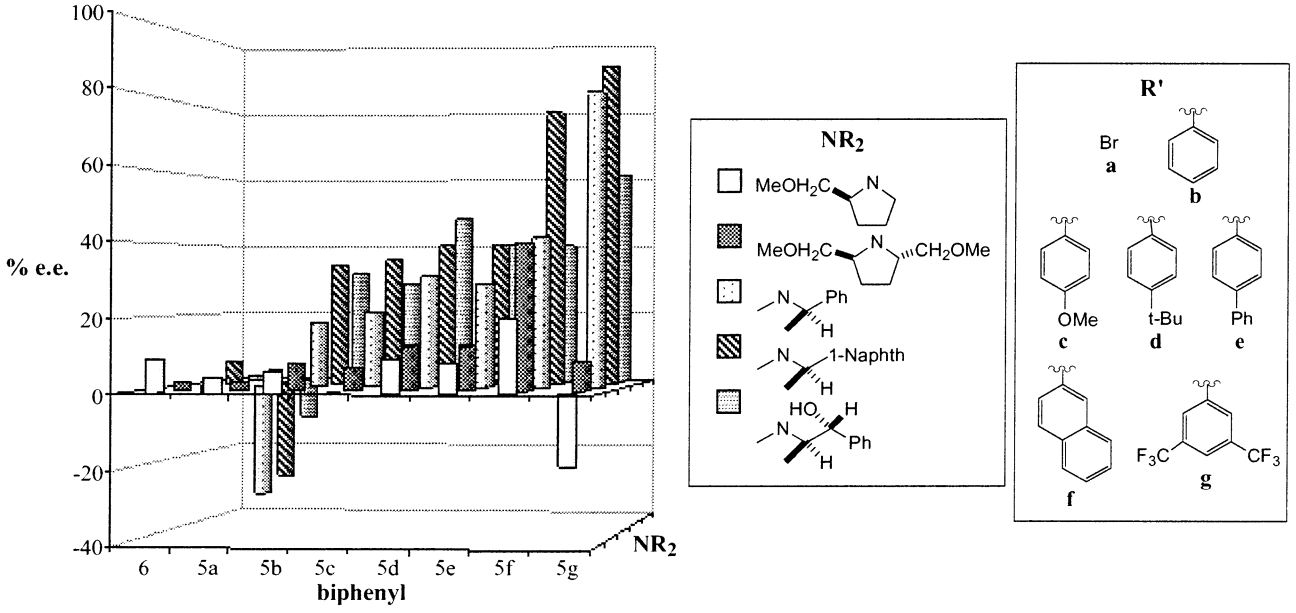
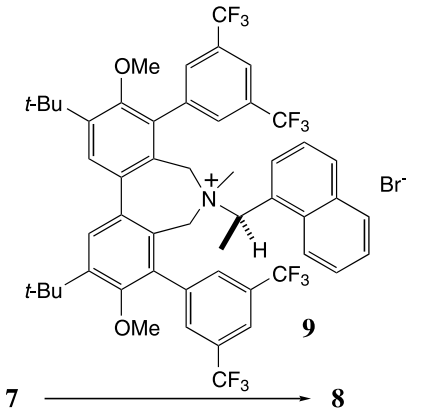


Figure 1. Screening of biphenyl PTC's in the alkylation of imine **5** (Scheme 3)

Table 1.

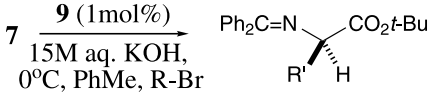


Mol% (**9**)	Base	Temp. (°C)	% E.e.[7]
1.0	9 M aq. KOH	30	91
1.0	9 M aq. KOH	20	94
1.0	9 M aq. KOH	10	94
1.0	12.5 M aq. KOH	20	94
1.0	12.5 M aq. NaOH	20	94
1.0	15 M aq. KOH	0	97
3.0	9 M aq. KOH	20	96
5.0	9 M aq. KOH	20	97

From these results it would appear that high levels of enantioselectivity can be obtained using 1 mol% catalyst, in conjunction with 9–15 M aq. KOH. These conditions are similar to those that we have previously found to be effective with cinchona alkaloid-derived phase-transfer catalysts[9] and are also similar to those commonly used with binaphthyl-derived quaternary ammonium salts.[2,10]

In order to test the utility of catalyst **9** further, the alkylation of imine **7** with a series of electrophiles was also examined (Table 2). High enantioselectivities were obtained and in all cases the reactions favoured the (*R*)-isomer.[12,13] The levels of selectivity observed are uniformly high and reaction times are short, which would seem to suggest that catalyst **9** may have considerable utility in the synthesis of α-amino acid derivatives.[11]

Table 2.



R-Br	Time (h)	% E.e.[12]	% Yield
$PhCH_2Br$	1.5	97	89
CH_2CHCH_2Br	2	94	83
CH_2CMeCH_2Br	1	95	100
CH_2CBrCH_2Br	2	93	77
2-NaphthylCH_2Br	1	96	97
$CHCCH_2Br$	1	89	71

In conclusion, we have demonstrated that a conformationally flexible biphenyl unit of type **1** can be utilised as a key component in the construction of asymmetric phase-transfer catalysts. This has led to the identification of a new quaternary ammonium salt **9** which gives high levels of enantioselectivity in the alkylation of glycine imine **7**. Further studies into the utility of catalysts of this type are underway and will be reported in due course.

Acknowledgements

We thank the EPSRC for funding and AstraZeneca for a studentship (to B.A.) and Dr. D. Levin for helpful discussions.

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7. Enantiomeric excess was determined by HPLC (Chiralcel OD-R, 60% acetonitrile/40% water, 0.5 ml/min) using racemic **8** (generated using *n*-Bu_4NBr as the PTC) as a control. Retention times observed were 45.0 min (*R*)-isomer and 49.2 min (*S*)-isomer.
8. Similar observations have been made with binaphthyl-derived catalysts.[2]
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12. E.e.'s were measured via HPLC using previously reported methods.[9]
13. Absolute stereochemistry was determined by comparison with previously prepared materials.[9] Preliminary experiments have shown that the (*S*)-amino acid derivatives can be prepared with similar levels of enantioselectivity by using the enantiomer of salt (**9**).