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Combining chiral elements in asymmetric phase-transfer catalysts: styrene oxide and chiral α,α-disubstituted pyrroline and piperidine derived structures

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Abstract—A new asymmetric phase-transfer catalyst, designed by combining the chiral building blocks styrene oxide and 2,5-dimethylpyrroline, is described. Catalytic testing using standard glycine imino ester alkylations shows good yields and moderate to good enantioselectivities with a surprising change in enantioselectivity over the course of the reaction. Alkylation of the β-hydroxyl group lead to catalysts with improved selectivity and a larger change in enantioselectivity during the reaction.

1. Introduction

Asymmetric phase-transfer catalysis offers a powerful method for many reactions, including the synthesis of unnatural amino acids.[1–8] Early work focused on Cinchona derivatives,[1–8] though recent reports have described successes with binaphthyl[1–7,9] and other[10–14] stereogenic centers. Marouka's state-of-the-art catalyst now gives remarkable results in a variety of phase-transfer catalyzed reactions, but is limited by a lengthy synthetic route.

We now present, a novel design approach in which we have multiple chiral centers derived from combining different chiral elements.[15] We have combined enantiopure styrene oxide, with chiral, α,α′-disubstituted amines, 2,5-dimethyl pyrroline, and 2,6-dimethylpiperidine;[16] following methylation, this yields catalysts with ammonium groups surrounded by three controlled chiral centers and a β-hydroxy group (Fig. 1). This provides two different influences on the catalyst–substrate interaction: the chiral β-alcohol and the chiral α-carbons on the amine ring. We hope that if the different groups are properly aligned, they may enhance substrate binding by working cooperatively, thus providing maximum enantioselectivity. In addition, our synthetic route is very direct, just two steps from amines prepared by literature methods.

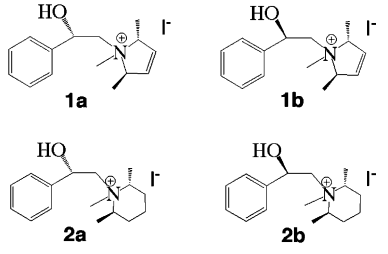

Figure 1. Catalysts **1a**,**b**, **2a**, and **2b**.

2. Results and discussion

Styrene oxide was chosen as a design element for its ready ability to combine with amines, the commercial availability of both pure enantiomers, and the β-alcohol left after ring opening. A hydroxyl group in a position to have an interaction with the substrate in addition to the electrostatic interaction has been hypothesized to be important to achieving selectivity dating back to the original Cinchona catalysts.[5,8] However, in our results, we found that the hydroxyl group was converted to an ether under catalysis conditions (vide infra).

2,5-Dimethylpyrroline and 2,5-dimethylpiperidine were chosen as the chiral amines because they have chiral

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centers α to the amine, bringing the asymmetry close to the ammonium center, which is presumably the primary point of binding with the enolate intermediate. The amines' C_2 symmetry insures that the ammonium itself will not be chiral, removing the possibility of additional uncontrolled stereocenters. Resolution of the racemic mixture of either amine allows access to both enantiomers, which in turn allows access to both diastereomeric pairs of the catalyst.[17,18]

Combination of the chiral moieties is accomplished by ring opening of the epoxide with the amine and a $Ca(OTf)_2$ catalyst (Fig. 2).[16] The synthesis is finished by reaction with MeI.[15] Column chromatography easily separates the quaternized product from any unreacted starting materials.

After initial catalytic trials showed a dramatic swing in enantioselectivity over the course of the one-hour reaction time, we devised alkylated catalysts **3**–**5**. Alkylated catalysts were synthesized under the same conditions that the catalytic trials were run, namely one hour at 0 °C with a 20-fold excess of alkyl halide (Fig. 3). We were surprised to have the reaction run to completion under such mild conditions, even with bulky alkyl halides such as 9-(bromomethyl)anthracene, but yields were uniformly good and ^{1}H NMR spectra showed no trace of starting material.

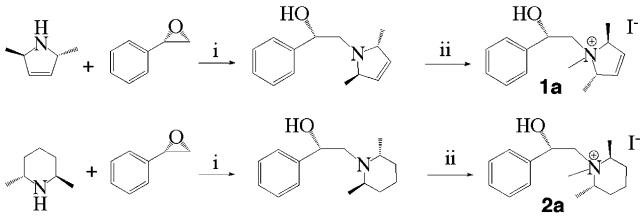

Figure 2. Synthetic scheme for catalysts **1** and **2**. (i) $Ca(OTf)_2$, MeCN, reflux 3 days. (ii) MeI, $CHCl_3$, reflux 3 days. Use of (*R*)-styrene oxide yields the isomers **1b** and **2b**.

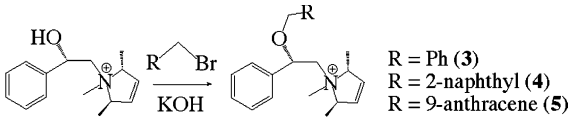

Figure 3. Synthetic scheme for catalysts **3**–**5**.

Table 1. Results of glycine imino ester alkylation with various alkyl halides at 0 °C

Entry	Catalyst	Alkyl halide	Solvent	Catalyst loading (%)	Time (min)	Enantioselectivity (ee%)[a]	Completion (%)
1	**1a**	2-(CH_3)BnBr	CH_2Cl_2	5	10	22.4	8.57
2	**1a**	2-(CH_3)BnBr	CH_2Cl_2	5	60	−34.7	100
3	**1a**	2-(CH_3)BnBr	Toluene	5	10	64.8	11.2
4	**1a**	2-(CH_3)BnBr	Toluene	5	60	−33.7	95.2
5	**1a**	2-(CH_3)BnBr	CH_2Cl_2	1	10	−18.6	23.2
6	**1a**	2-(CH_3)BnBr	CH_2Cl_2	1	60	21.7	67.7
7	**1a**	BnBr	CH_2Cl_2	1	10	−0.5	41.9
8	**1a**	BnBr	CH_2Cl_2	1	60	−5.8	72.4
9	**1a**	4-(CH_3)BnBr	CH_2Cl_2	5	10	7.0	2.0
10	**1a**	4-(CH_3)BnBr	CH_2Cl_2	5	60	21.5	88.2
11	**1a**	MeI	CH_2Cl_2	5	10	12.3	3.7
12	**1a**	MeI	CH_2Cl_2	5	60	9.8	84.7
13	**1a**	Allyl Br	CH_2Cl_2	5	10	21.2	3.1
14	**1a**	Allyl Br	CH_2Cl_2	5	60	18.7	39.7
15	**1b**	2-(CH_3)BnBr	CH_2Cl_2	5	20	21.9	68.3
16	**1b**	2-(CH_3)BnBr	CH_2Cl_2	5	60	−11.1	92.8
17	**1b**	2-(CH_3)BnBr	Toluene	5	10	50.3	33.3
18	**1b**	2-(CH_3)BnBr	Toluene	5	60	5.6	88.3
19	**1b**	BnBr	Toluene	5	10	49.1	50.8
20	**1b**	BnBr	Toluene	5	60	49.4	75.5
21	**1b**	4-(CH_3)BnBr	CH_2Cl_2	5	10	−81.0	18.9
22	**1b**	4-(CH_3)BnBr	CH_2Cl_2	5	60	−13.0	67.9
23	**1b**	Allyl Br	CH_2Cl_2	5	10	1.4	9.3
24	**1b**	Allyl Br	CH_2Cl_2	5	60	−0.5	38.9
25	**1b**	MeI	CH_2Cl_2	5	10	0.7	1.4
26	**1b**	MeI	CH_2Cl_2	5	60	−2.5	88.1
27	**2a**	BnBr	CH_2Cl_2	5	10	38.7	9.4
28	**2a**	BnBr	CH_2Cl_2	5	60	−23.8	62.1
29	**2a**	2-(CH_3)BnBr	CH_2Cl_2	5	10	30.5	10.2
30	**2a**	2-(CH_3)BnBr	CH_2Cl_2	5	60	−22.6	63.4
31	**2b**	BnBr	CH_2Cl_2	5	10	−32.1	27.3
32	**2b**	BnBr	CH_2Cl_2	5	60	−6.2	64.1
33	**2b**	2-(CH_3)BnBr	CH_2Cl_2	5	10	38.6	6.0
34	**2b**	2-(CH_3)BnBr	CH_2Cl_2	5	60	−43.5	58.2

[a] Enantioselectivity and completion determined by HPLC on a Chiracel OD-H column. Negative enantioselectivities refer to selectivity for the opposite enantiomer.

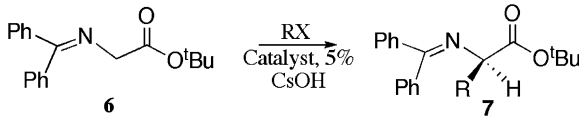

Figure 4. General scheme for glycine imino ester alkylation.

Catalytic competency was established using standard literature procedures for the alkylation of glycine imino ester **6** (Fig. 4).[15] Initial results using the hydroxyl catalysts **1a**, **b**, **2a**, and **2b** showed promising enantioselectivity, but also a surprising change in enantioselectivity over time (Table 1). This was not a simple degradation toward a racemic mixture, but rather a change in preference from one product enantiomer to the other. For example, the enantioselectivity for alkylation with 2-methylbenzyl bromide (entries 3 and 4) at 10 min is nearly 65% ee, but at 60 min is almost 34% ee for the opposite enantiomer. While this effect is not observed for all halides, it is interesting and led us to consider possible mechanisms.

The obvious route for a change in the catalyst is alkylation of the hydroxyl group, which removes a potential site for substrate binding and simultaneously changes the steric environment. The potential of this change was explored by establishing that alkylation does take place under catalysis reaction conditions (vide supra). Thus, compounds **3**–**5** were synthesized to create a family with increasing steric bulk attached to the oxygen (Fig. 3). However, alkylation did not stop the enantioselectivity swing; quite to the contrary an even larger swing in enantioselectivity was observed with both the benzyl (**3**) and methylnaphthyl (**4**) derivatives (Table 2, see entries 1 and 2 or 13 and 14). The 9-methylanthracene derivative **5** showed almost no enantioselectivity, so correspondingly no swing was observed. The large size of the anthracenyl group may prohibit close contact between the catalyst and enolate, removing any pathway for selectivity.

Perhaps, the change in selectivity could be explained by the buildup of bromide ion as the reaction progressed. To test this possibility, we added CsBr (30 equiv) to the reaction mixture (Table 2, entries 23–26). The shift in selectivity was indeed muted, but the larger enantioselectivity observed at the end of the reaction was not observed. Thus, the counterion may play a role in the function of the catalyst, but it is only a contributing factor.

3. Conclusions

A new design for asymmetric phase-transfer catalysts has been discussed, and the synthetic scheme and catalytic competency established. In addition to decent enantioselectivities, an interesting shift in enatioselectivity during the reaction was observed. Alkylation of the β-hydroxyl group was established to occur under reaction conditions, but this was not responsible for the enantioselectivity shift.

Table 2. Results of glycine imino ester alkylation with various alkyl halides at 0 °C using alkylated catalysts **3**–**5**

Entry	Catalyst	Alkyl halide	Solvent	Catalyst loading (%)	Time (min)	Enantioselectivity (ee%)[a]	Completion (%)
1	**3**	BnBr	CH_2Cl_2	5	10	66.4	20.8
2	**3**	BnBr	CH_2Cl_2	5	60	−51.1	100
3	**3**	2-(CH_3)BnBr	CH_2Cl_2	5	10	39.4	7.15
4	**3**	2-(CH_3)BnBr	CH_2Cl_2	5	60	−58.6	100
5	**3**	4-(CH_3)BnBr	CH_2Cl_2	5	10	21.4	6.1
6	**3**	4-(CH_3)BnBr	CH_2Cl_2	5	60	23.2	100
7	**3**	BnBr	Toluene	0.5	10	−8.7	5.1
8	**3**	BnBr	Toluene	0.5	120	2.4	59.0
9	**3**	2-(CH_3)BnBr	Toluene	0.5	10	−14.2	2.6
10	**3**	2-(CH_3)BnBr	Toluene	0.5	120	1.6	50.6
11	**4**	BnBr	CH_2Cl_2	5	10	2.5	5.7
12	**4**	BnBr	CH_2Cl_2	5	60	−29.1	83.5
13	**4**	2-(CH_3)BnBr	CH_2Cl_2	5	10	66.7	5.4
14	**4**	2-(CH_3)BnBr	CH_2Cl_2	5	60	−68.9	63.4
15	**4**	BnBr	Toluene	0.5	10	−32.0	0.6
16	**4**	BnBr	Toluene	0.5	240	4.4	75.0
17	**4**	2-(CH_3)BnBr	Toluene	0.5	10	95.4	15.6
18	**4**	2-(CH_3)BnBr	Toluene	0.5	120	−29.8	59.0
19	**5**	BnBr	Toluene	0.5	10	−3.5	4.5
20	**5**	BnBr	Toluene	0.5	120	1.7	54.2
21	**5**	2-(CH_3)BnBr	Toluene	0.5	10	−21.6	4.6
22	**5**	2-(CH_3)BnBr	Toluene	0.5	120	6.1	60.2
23	**4**	2-(CH_3)BnBr–CsBr	CH_2Cl_2	5	10	−26.4	11.6
24	**4**	2-(CH_3)BnBr–CsBr	CH_2Cl_2	5	60	−23.0	100
25	**4**	2-(CH_3)BnBr–CsBr	Toluene	0.5	10	−36.9	11.8
26	**4**	2-(CH_3)BnBr–CsBr	Toluene	0.5	120	−26.5	100

[a] Enantioselectivity and completion determined by HPLC on a Chiracel OD-H column. Negative enantioselectivities refer to selectivity for the opposite enantiomer.

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Supplementary data

Included within the supplemental data are detailed procedures and spectroscopic data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.141.

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