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# Combining chiral elements: a novel approach to asymmetric phase-transfer catalyst design

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**Abstract**—A new dicationic asymmetric phase-transfer catalyst, designed by combining chiral elements, is described. Catalytic testing using standard glycine imino ester alkylations shows good yields and moderate enantioselectivities.

## 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,[9–14] though recent reports have described successes with binaphthyl[15–22] and other[23–26] stereogenic centers. Most work has utilized a single ammonium group on the catalyst, with a few notable exceptions.[27,28] Our group's interest is in dicationic catalysts,[29,30] hypothesizing that with the proper alignment of the ammonium centers, a 'reverse chelate' effect may be observed in which the nucleophilic anion interacts with both ammonium centers to provide optimum enantioselectivity.

We now present a novel design approach in which multiple chiral centers are brought together from combining different chiral elements (Fig. 1). The chiral elements in our design are tartaric acid (from earlier work[30]) and 2,5-dimethylpyrroline rings. Using resolved pyrrolines, two diastereomeric catalysts (one of each enantiomeric pair) have been synthesized and their catalytic competence in glycine imino ester alkylation established.

## 2. Results and discussion

Tartaric acid was chosen as the backbone because (1) its derivatives have a successful history in inducing asymmetry in other catalytic processes,[31–33] (2) it allows us to develop a dicationic catalyst, and (3) it is an inexpensive source of optically active carbons. We were encouraged by the relatively good enantioselectivities reported in recent publications by Shibasaki that use the same tartaric acid stereocenters as in our design.[27,34] However, the synthesis described by Shibasaki is limited to attaching carbon groups to the nitrogen from primary alkyl halides.[27] We have previously reported an improved synthesis that allows for the introduction of secondary amines,[30] and we have adapted our earlier synthetic scheme to the amines presented here (Fig. 2). The key intermediate in the synthetic scheme is acid chloride **3**, which reacts with secondary amines to form amides that can be reduced with LAH. Quaternization is affected with methyl triflate.

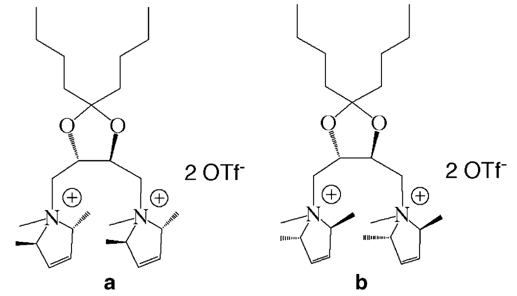

**Figure 1.** Structures of catalysts **1a** and **1b**.

2,5-Dimethylpyrroline **7** was chosen as the chiral amine because it has chiral centers α to the amine, bringing the stereocenters close to the ammonium, which is presumably the point of association with the enolate

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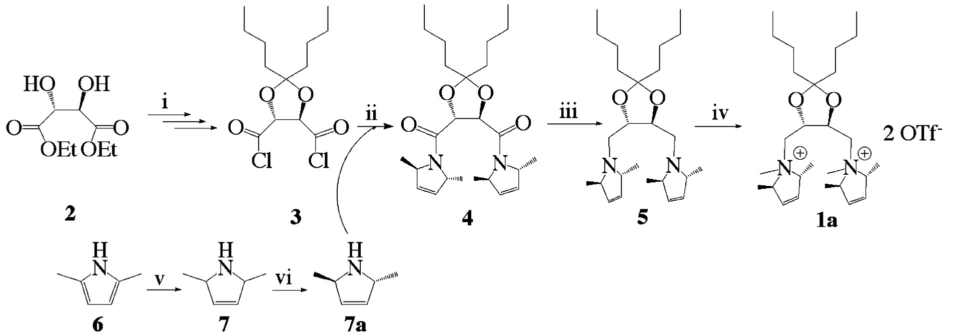

**Figure 2.** Synthetic scheme for synthesis of catalysts **1a** and **1b**. Reagents and conditions: (i) (1) nonanone, HTos, distillation, (2) LiOH, MeOH, (3) TMSCl, THF, (4) oxalyl chloride, DMF, THF; (ii) 2,5-(*R*,*R*)-dimethylpyrroline (**7a**), $NEt_3$; (iii) LAH, THF, reflux 16 h; (iv) MeOTf, $CHCl_3$, 16 h; (v) Zn/HCl; (vi) (+)-camphorsulfonic acid.

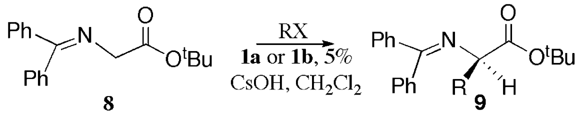

**Figure 3.** General scheme for glycine imino ester alkylation.

intermediate. Its $C_2$ symmetry insures that the ammonium itself will not be chiral, removing the possibility of additional uncontrolled stereocenters. Synthesis of **7** by Zn/HCl reduction of dimethyl pyrrole yields a mixture of stereoisomers;[35] resolution of the racemic mixture[36] with camphorsulfonic acid, commercially available in both enantiomers, allows access to both pyrroline enantiomers (e.g., **7a**), which in turn allows access to both diastereomeric enantiomer pairs of the catalyst.

The nonanone ketal provides two four-carbon 'tails.' These provide a non-polar element to the structure that enhances catalyst solubility in organic solvents. We are

**Table 1.** Results of glycine imino ester alkylation with various alkyl halides at 0 °C in $CH_2Cl_2$

| Entry | Catalyst | Alkyl halide | Time (min) | Enantioselectivity (ee, %)[a] | Completion (%) |
|---|---|---|---|---|---|
| 1 | **1a** | BnBr | 60 | 32.4 | 54.6 |
| 2 | **1b** | BnBr | 60 | 13.1 | 68.3 |
| 3 | **1a** | Allyl Br | 60 | −4.4 | 61.4 |
| 4 | **1b** | Allyl Br | 10 | 3.5 | 56.7 |
| 5 | **1a** | 2-MeBnBr | 10 | 27.5 | 57.6 |
| 6 | **1a** | 2-MeBnBr | 60 | 21.7 | 59.4 |
| 7 | **1b** | 2-MeBnBr | 10 | 33.4 | 63.7 |
| 8 | **1b** | 2-MeBnBr | 60 | 22.3 | 67.5 |
| 9 | **1a** | 4-MeBnBr | 60 | 28.0 | 60 |
| 10 | **1b** | 4-MeBnBr | 60 | 26.6 | 63.5 |
| 11 | **1a** | MeI | 10 | 0.2 | 59 |
| 12 | **1b** | MeI | 10 | 7.6 | 69.4 |
| 13 | **1a** | BrMeNaphthyl | 150 | 21.3 | 90.5 |
| 14 | **1b** | BrMeNaphthyl | 150 | 12.9 | 86.9 |

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

**Table 2.** Results of glycine imino ester alkylation with various alkyl halides at −45 °C in $CH_2Cl_2$ after reaction for 10 h

| Entry | Catalyst | Alkyl halide | Enantioselectivity (ee, %)[a] | Completion (%) |
|---|---|---|---|---|
| 1 | **1a** | Allyl Br | 28 | 75 |
| 2 | **1b** | Allyl Br | −28 | 72 |
| 3 | **1a** | MeI | 8 | 73 |
| 4 | **1b** | MeI | −8 | 50 |
| 5 | **1a** | 2-($CH_3$)BnBr | 26 | 85 |
| 6 | **1b** | 2-($CH_3$)BnBr | 9 | 77 |
| 7 | **1a** | 4-($CH_3$)BnBr | 19 | 84 |
| 8 | **1b** | 4-($CH_3$)BnBr | −27 | 80 |
| 9 | **1a** | BnBr | 30 | 73 |
| 10 | **1b** | BnBr | 26 | 47 |
| 11 | **1a** | 2-($BrCH_2$)naphthalene | −12 | 39 |
| 12 | **1b** | 2-($BrCH_2$)naphthalene | −37 | 45 |

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

currently working on alternative 'tails' including the methyl–$^t$butyl set that Shibasaki[29] has reported.

Catalytic competency was established using standard literature procedures for the alkylation of glycine imino ester **8** (Fig. 3). Results at two different reaction temperatures are given in Tables 1 and 2.

Glycine imine alkylation results shown in Tables 1 and 2 demonstrate that both diastereomers of our catalyst are effective catalysts. We can draw several conclusions: (1) Under 'warm' conditions (0 °C), modest enantioselectivities are observed for a variety of substrates. (2) Enantioselectivities are different, but not opposite, for the diastereomers (see Table 1, entries 1 and 2, e.g.), though there are some coincidental opposites. This is expected, as the stereocenters work cooperatively in one diastereomer, but not in the other. (3) Enantioselectivity is best at the beginning of a reaction (compare Table 1, entries 5 and 6 or 7 and 8). (4) Lowering the reaction temperature did not dramatically increase selectivity. Attempts at catalysis at lower temperatures than −45 °C lead to no reaction.

## 3. Conclusions

A new design for asymmetric phase-transfer catalysts has been discussed, and the synthetic scheme and catalytic competency established. Modest enantioselectivities were observed in the alkylation of a glycine imino ester. Further work on optimization of the catalyst design is underway.

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## Supplementary data

The supplementary data is available online with the paper in ScienceDirect. 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.2005.06.084.

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