

# Plagiarizing Proteins: Enhancing Efficiency in Asymmetric Hydrogen-Bonding Catalysis through Positive Cooperativity\*\*

Christopher R. Jones, G. Dan Pantoş, Angus J. Morrison, and Martin D. Smith\*

Nature achieves nearly catalytic perfection in enzymes through the juxtaposition of specific functional groups in space.<sup>[1]</sup> Although the effects that contribute to the remarkable rate acceleration observed in enzyme-catalyzed reactions are manifold, it has been proposed that mutually reinforcing, or cooperative noncovalent interactions<sup>[2]</sup> within a receptor can play a significant role.<sup>[3]</sup> This tenet has been postulated to be a factor in the extraordinary avidity of binding in systems such as streptavidin–biotin, and has been elegantly applied in the generation of synthetic receptors with enhanced anion-binding properties.<sup>[4]</sup> In a catalyst system with positively cooperative binding, the enthalpic contribution to the transition-state binding energy may be increased through a reduction in dynamic behavior, resulting in stronger noncovalent interactions within the catalyst structure. This can outweigh the entropic cost of the associated reduction in motion, and hence lead to tighter transition-state binding, and a subsequent increase in catalytic efficiency. We considered whether this effect—which is implicated in the remarkable efficiency exhibited by some enzymes—could be exploited in the development of more efficient asymmetric catalysts that operate by hydrogen bonding.<sup>[5]</sup> This could lead to the development of new transformations through the discovery of more active catalysts with lower loading, shorter reaction times, and wider substrate scope. In designing these new catalysts, we reasoned that by analogy with ligand–protein binding, a series of noncovalent interactions within the catalyst structure could: 1) direct folding toward population of an ensemble of structured conformations, preorganizing the catalyst and minimizing the entropic cost of transition-state (TS) binding,<sup>[3,6]</sup> and 2) result in stronger intramolecular noncovalent interactions and cooperative ligand binding and

hence greater stabilization of charged intermediates and transition states.<sup>[7–9]</sup>

Herein we generate conformationally well-defined but flexible thiourea catalysts<sup>[10,11]</sup> that benefit from cooperative ligand binding, and we demonstrate the utility of this phenomenon in catalytic asymmetric synthesis. We have constructed a simple and effective turn mimetic that populates a well-defined hairpin conformation in solution and in the solid state stabilized by intramolecular hydrogen bonds.<sup>[12]</sup>

A major aim of the design and generation of well-defined unnatural folded materials<sup>[13]</sup> is the evolution of function similar to that observed in natural biopolymers. It has been demonstrated through a series of elegant studies that folded peptidic materials can be highly effective asymmetric catalysts for a range of synthetic transformations.<sup>[14]</sup> Our catalyst scaffold, which can be easily and efficiently prepared, is depicted in Figure 1.<sup>[15]</sup>

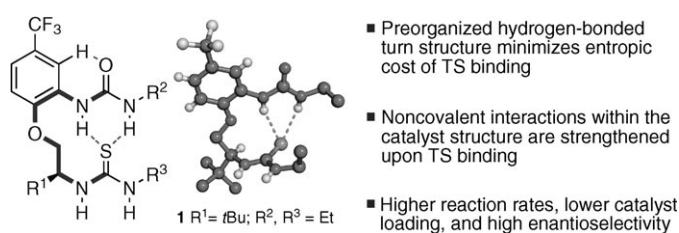


Figure 1. Rationale behind the catalyst design.

The conformation of materials incorporating this construct have been extensively probed in solution and in the solid state.<sup>[9]</sup> NMR studies of model compound 1 (in an aprotic solvent) confirmed the presence of a series of intramolecular hydrogen bonds consonant with a turn conformation and indicated that the *trans,trans* thiourea conformation is populated;<sup>[16,17]</sup> this is consistent with the X-ray structure of 1 (Figure 1).<sup>[18,19]</sup> In general, for these scaffolds to populate turn conformations where R<sup>3</sup> is relatively large, we have found that a small R<sup>2</sup> group (in the case of 1, an ethyl group) is optimal. The turn construct is insensitive to the size of the R<sup>1</sup> group, but the absolute configuration at this center can have important implications when other chiral substituents are appended to this scaffold.

With a reliable turn-forming design in hand, we turned our attention to investigating the potential utility of the cooperativity concept in asymmetric catalysis. Our initial investigations focused on the ability of these materials to mediate reactions involving *N*-*tert*-butoxycarbonyl (*N*-Boc) aldimines as substrates, and hence we first examined a model Mannich reaction with a silyl ketene acetal nucleophile.<sup>[20,21]</sup>

[\*] Dr. M. D. Smith  
Chemistry Research Laboratory, University of Oxford  
12 Mansfield Road, Oxford OX1 3TA (UK)  
E-mail: martin.smith@chem.ox.ac.uk  
Homepage: <http://msmith.chem.ox.ac.uk>  
C. R. Jones, Dr. G. Dan Pantoş  
Department of Chemistry, University of Cambridge  
Lensfield Road, Cambridge CB2 1EW (UK)  
Dr. A. J. Morrison  
Schering Plough Corporation  
Newhouse, Lanarkshire, Scotland ML1 5SH (UK)

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We reasoned that exploring a known reaction manifold would enable us to benchmark the effectiveness of our folded catalysts against materials known to be proficient in this reaction and enable evaluation of our catalyst design blueprint. A preliminary screen of thiourea catalysts indicated that materials bearing a pyrrolyl-1,2-diamine substituent<sup>[22]</sup> were most effective, and hence we generated the small library of compounds **2–6** based on this template (Figure 2). Catalysts containing two urea functional groups were also prepared and evaluated, but these were found to be significantly less effective.<sup>[23]</sup>

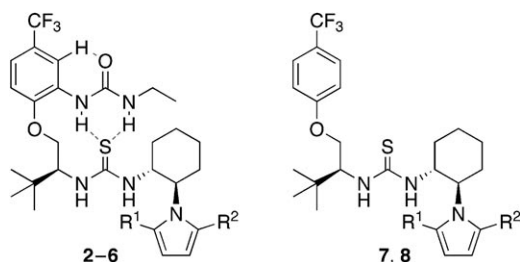


Figure 2. Catalysts examined in this study.

We also generated a series of control catalysts **7** and **8** that do not bear the intramolecular hydrogen-bond-donor group to investigate the effect of this deletion on asymmetric induction and catalytic activity. The efficacy of materials **2–8** in mediating the asymmetric Mukaiyama–Mannich reaction at a loading of 5 mol % is outlined in Table 1. Our investigations demonstrate that the size of the substituents on the pyrrole is paramount in determining the effectiveness of the asymmetric induction, with **4** ( $R^1 = \text{Me}$ ,  $R^2 = \text{Ph}$ ) affording *R* product in 97 % yield with greater than 99 % *ee*.<sup>[24,25]</sup>

Table 1: Catalyst screening with a Mukaiyama–Mannich reaction.<sup>[a]</sup>

| Catalyst (5 mol %)<br>48 h, –40 °C, toluene |       |            |                          |                              |
|---------------------------------------------|-------|------------|--------------------------|------------------------------|
|                                             |       |            |                          |                              |
| Cat.                                        | $R^1$ | $R^2$      | Yield [%] <sup>[b]</sup> | <i>ee</i> [%] <sup>[c]</sup> |
| <b>2</b>                                    | Ph    | Ph         | 70                       | 9                            |
| <b>3</b>                                    | Me    | Me         | 97                       | 95                           |
| <b>4</b>                                    | Me    | Ph         | 97                       | > 99                         |
| <b>5</b>                                    | Me    | 1-naphthyl | 81                       | > 99                         |
| <b>6</b>                                    | Me    | 2-naphthyl | 77                       | 91                           |
| <b>7</b>                                    | Me    | Ph         | 72                       | 95                           |
| <b>8</b>                                    | Me    | Me         | 71                       | 91                           |

[a] Reaction conditions: 0.25 mmol **9**, 0.5 mmol ketene acetal, 0.2 mL toluene. [b] Yield of isolated product. [c] Measured by HPLC on a chiral stationary phase. TBS = *tert*-butyldimethylsilyl.

With an optimal catalyst for this reaction, we investigated the generality of this method by preparing a series of substituted  $\beta$ -aryl  $\beta$ -amino acids using catalyst **4** at different loadings. This demonstrated that catalyst **4** is uniformly effective in mediating reactions with either electron-donating

groups or electron-withdrawing groups on the aldimine at a loading of 5 mol %, generating products with universally high enantioselectivity (97 to > 99 % *ee*) and yield (Table 2).

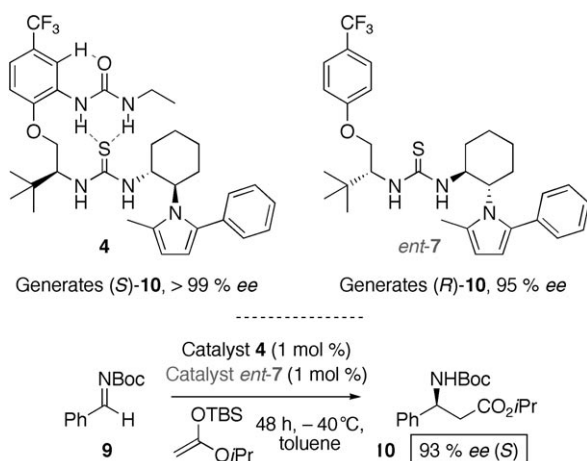
Table 2: Mannich reactions at different catalyst loadings.<sup>[a]</sup>

| $R^1$             | 0.1 mol % Loading <sup>[b]</sup> |                              | 1 mol % Loading <sup>[c]</sup> |                              | 5 mol % Loading <sup>[c]</sup> |                              |
|-------------------|----------------------------------|------------------------------|--------------------------------|------------------------------|--------------------------------|------------------------------|
|                   | Yield [%] <sup>[d]</sup>         | <i>ee</i> [%] <sup>[e]</sup> | Yield [%] <sup>[d]</sup>       | <i>ee</i> [%] <sup>[e]</sup> | Yield [%] <sup>[d]</sup>       | <i>ee</i> [%] <sup>[e]</sup> |
| H                 | 75                               | 99                           | 96                             | > 99                         | 97                             | > 99                         |
| 4-Me              | 63                               | 81                           | 79                             | 95                           | 97                             | 97                           |
| 1-naphthyl        | 81                               | 93                           | 86                             | 96                           | 84                             | 98                           |
| 4-OMe             | 40                               | 84                           | 85                             | 94                           | 83                             | 98                           |
| 3-NO <sub>2</sub> | 75                               | 93                           | 74                             | 99                           | 73                             | > 99                         |

[a] Reaction conditions: 0.5 mmol imine, 1 mmol ketene acetal, 0.4 mL toluene. [b] Reaction time: 96 h. [c] Reaction time: 48 h. [d] Yield of isolated product. [e] Determined by HPLC on a chiral stationary phase.

When the loading of **4** was reduced to 1 mol %, the excellent levels of enantioselectivity were maintained (94 to > 99 % *ee*) and the yield of isolated product decreased only slightly. Remarkably, the catalyst loading of **4** can be reduced to 0.1 mol % whilst maintaining high enantioselectivity (for  $R^1 = \text{H}$ , 3-NO<sub>2</sub>, 1-naphthyl); less reactive imines ( $R^1 = 4\text{-Me}$ , 4-OMe) give lower *ee* values at this loading.<sup>[26,27]</sup> These loadings are significantly lower than the 5–10 mol % generally required in thiourea-catalyzed transformations, and confirm that optimum catalyst **4** is both catalytically proficient and highly enantioselective. The materials **7** and **8**, in which the intramolecular urea hydrogen-bond donor is absent (Table 1), produced **10** in 72 % yield (95 % *ee*) and 71 % yield (91 % *ee*), respectively, at a loading of 5 mol %. This indicates that the effect of conformational ordering on asymmetric induction (through the internal bifurcated hydrogen bond) is significant but relatively small.

To probe catalyst efficiency rather than asymmetric induction we need to investigate kinetic parameters—and hence we instigated a series of catalyst competition experiments (Scheme 1). A competition experiment between 1 mol % **4** (known to generate *S*-configured material) and 1 mol % *ent*-**7** (known to generate *R*-configured material) afforded material **10** with 93 % *ee* (*S*) and 97 % yield, indicating that catalyst **4** significantly outcompetes catalyst *ent*-**7** for substrate in this specific reaction.<sup>[28,29]</sup> We attribute this dramatic rate enhancement to tighter ligand–receptor binding in the transition state as a result of strengthened noncovalent interactions within the catalyst structure in **4** that are absent in **7**. To support this premise, we compared the anion-binding ability<sup>[30]</sup> of **3** and **8** to establish that the noncovalent interactions within the catalyst structure are mutually reinforcing.<sup>[31]</sup> According to the cooperative model, intrareceptor interactions could make a significant contribution to complex stability. These studies were carried out in



**Scheme 1.** Reaction conditions: 0.25 mmol **9**, 0.5 mmol ketene acetal, 0.2 mL toluene.

$\text{CDCl}_3$  at  $-15^\circ\text{C}$  using tetra-*N*-butylammonium chloride as the anion source, and are consistent with ligand–receptor stoichiometry of 1:1 for both **3** and **8**. Conformational studies on the anion-bound catalyst **3** indicate population of the *trans,trans* thiourea conformer, similar to what is observed for the ground-state conformation of **1**. This may indicate that the turn scaffold affects the conformational propensities of the thiourea portion of the catalyst.<sup>[17]</sup> Catalyst **3** was found to have  $K_a = (550 \pm 85) \text{ M}^{-1}$  towards chloride anion, while model compound **8**, containing a single urea functionality, has a  $K_a$  less than  $10 \text{ M}^{-1}$ . Hence **3** has a binding constant for chloride anion approximately two orders of magnitude larger than that for **8**, entirely consistent with the tenet of cooperative ligand binding outlined earlier, and reflected in the significantly increased catalytic efficiency of this material.<sup>[32]</sup>

In this study we have outlined the synthesis of conformationally well-defined thiourea catalysts designed to mimic the positively cooperative action of enzymes. We have demonstrated that noncovalent interactions within a  $\beta$ -turn catalyst structure lead to significantly higher levels of catalytic efficiency in a model Mukaiyama–Mannich reaction than noncooperative materials. This increased cooperativity-led efficiency is reflected in turnover rates and catalyst loading, and is coupled with extremely high enantioselectivities. We believe that this nature-inspired cooperative design may have utility in the development of highly efficient catalysts for demanding asymmetric transformations.

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