

Divergent Stereoinduction Mechanisms in Urea-Catalyzed Additions to Imines

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Abstract: Catalyst structure/enantioselectivity profiles for the asymmetric Strecker and Mannich reactions were obtained through systematic variation of each modular component of the catalyst. Although the thiourea derivative **1** afforded optimal results in both reactions (97–98% ee), the structural elements responsible for stereoinduction were found to be fundamentally different. Insights gleaned from these studies led to the development of a new generation catalyst for the Mannich reaction that promotes the asymmetric silyl ketene acetal addition to *N*-Boc benzaldimine in 94% ee. The new catalyst is a simple amino acid derivative possessing less than half the molecular weight and two fewer stereocenters relative to **1**.

Key words: asymmetric catalysis, organocatalysis, nucleophilic additions, imines, substituent effects

Nature is the principal expert practitioner of asymmetric synthesis, and accordingly serves as both a model and an inspiration for the design of synthetic chiral catalysts. While enzymes exploit several types of interactions between active site and substrate to effect high levels of stereoinduction, the identification of highly enantioselective reactions catalyzed by proline¹ and other remarkably simple organic catalysts^{2,3} has raised the question of what constitute the minimal functional and structural features required for efficient asymmetric catalysis.⁴ Herein we report a systematic investigation of structure–enantioselectivity relationships in an organic catalyst system for imine addition reactions. This effort has led to the discovery that a chiral urea catalyst operates by fundamentally different stereoinduction mechanisms in the activation of related imine substrates, and to the identification of an extraordinarily simple and effective new catalyst for the addition of silyl ketene acetals to *N*-Boc-protected aldimines (the Mannich reaction).

In 1998, we described a parallel-library approach to the discovery of catalysts for the asymmetric hydrocyanation of imines (the Strecker reaction).^{5a} Through a combination of empirical and structure-based optimization studies, thiourea derivative **1** and closely related analogs were identified as highly general and effective catalysts for the asymmetric hydrocyanation of *N*-allyl or *N*-benzyl aldimines^{5a,b,e} and ketoimines (Scheme 1, Equation 1).^{5c} Subsequently, it was discovered that the same catalysts

are applicable to the asymmetric Mannich reaction of *N*-Boc aldimines with silyl ketene acetals (Scheme 1, Equation 2).⁶ Despite the fact that these two reactions are catalyzed with nearly perfect enantioselectivity by the same catalyst, the *N*-Boc aldimine substrates utilized in the Mannich reaction are sterically and electronically different from the *N*-alkyl imines used in the Strecker reaction. Therefore, the same mechanism of stereoinduction could not be assumed.⁷ With this in mind, we undertook an investigation of the correlation between catalyst structure and enantioselectivity for both the Strecker and Mannich reactions, systematically varying the amide, amino acid, urea, diamine, and salicylaldimine elements in order to develop a comparative stereoinduction profile.

The effect of modifications to the amide bond and urea moieties of catalyst **1** on the two model reactions is illustrated in Table 1.⁸ In general, use of thiourea (Y = S) rather than urea (Y = O) derivatives resulted in improved enantioselectivity for both the Mannich and Strecker reactions, although this effect was more pronounced for the former.⁹ For example, thiourea catalyst **4** catalyzed the Mannich reaction in 97% ee, while urea analog **5** afforded only 82% ee (*vis* 98% vs. 97% ee in the Strecker reaction).¹⁰ Enhanced enantioselectivity was also observed in both reactions with catalysts bearing a tertiary, rather than secondary, amide.⁹ Again, this effect is more pronounced in the case of the Mannich reaction (Table 1, catalysts **1** vs. **2**). The steric properties of the tertiary amide substituents were important in both reactions, but with opposing trends. *N,N*-Dimethyl amide catalyst **6** proved to be one of the best catalysts for the Strecker reaction (99% ee), but was only moderately effective in the case of the Mannich reaction (86% ee). The more sterically demanding *N,N*-diisobutyl derivative **8** afforded improved ee in the case of the Mannich reaction (93% ee), but poorer results in the Strecker reaction (95% ee). In both reactions, use of an ester moiety in place of the amide bond resulted in a reduction in enantioselectivity (**10** vs. **3**).

The identity of the amino acid proved to be critical in the Mannich reaction (Table 2). Whereas *tert*-leucine derivatives afforded best results, substitution with valine or alanine led to abrupt decreases in enantioselectivity (**1** vs. **11** and **12**). Incorporation of the aromatic amino acid phenylglycine (catalyst **13**) also resulted in diminished ee's. Increasing the steric properties of the amino acid substituent beyond those of *tert*-leucine, as in catalyst **14**, also led to a reduction in enantioselectivity relative to **1**, al-

though only to a moderate extent. In contrast, the performance of the Strecker reaction is remarkably insensitive to the identity of the amino acid. Decreasing the size of the amino acid substituent from *tert*-butyl to methyl resulted in highly enantioselective catalysis (>90% ee, catalyst **12**). Phenylglycine- (**13**) and 2-amino-3-methyl-3-phenyl-butyric acid (**14**)-derived catalysts – while not superior to **1** – also serve as effective catalysts for the Strecker reaction.

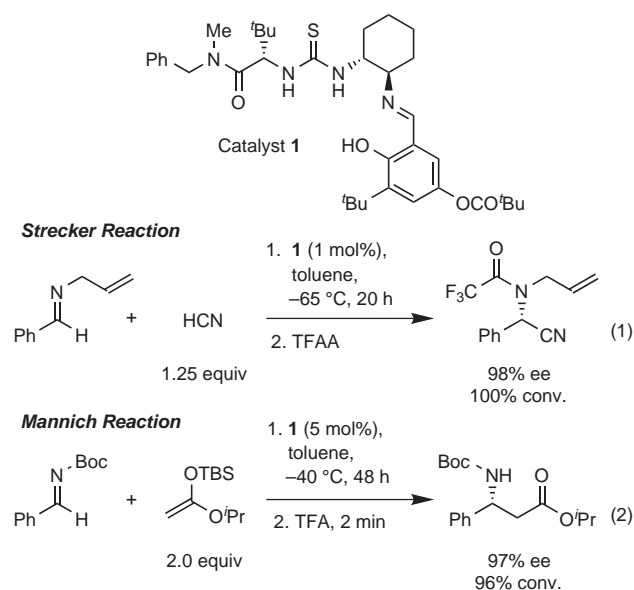
A study of the effect of modifications to the salicylaldimine portion of the catalyst on enantioselectivity also revealed dramatic differences between the two reactions (Table 3). In general, the Strecker reaction proved to be sensitive to subtle variations in the salicylaldimine substituents. While decreasing the size of the *ortho*-substituent (R^2) had a minor effect on ee (**15–17**), modification of the *para*-substituent (R^3) resulted in diminished enantioselectivity (**15** vs. **1**).¹¹ Methylation of the phenol ($R^1 = \text{Me}$, **19** vs. **15**), or substitution with 1-hydroxyl-2-naphthalaldimine (**20**), also led to significant reductions in the enantioselectivity of the Strecker reaction. In contrast, asymmetric induction in the Mannich reaction was virtually insensitive to salicylaldimine modification, with negligible dependence on R^2 (**15–17**) and none on R^3 (**1** vs. **15**).¹² Although lower enantioselectivity was observed in toluene with catalyst **20**, this could be attributed to low catalyst solubility. Replacing the solvent with THF, which is generally an effective solvent for the Mannich reaction (Table 1, **1**), led to complete solubilization of **20** and outstanding enantioselectivity in the Mannich reaction (98% ee).¹³ As in the case of the Strecker reaction, methylation of the phenol ($R^1 = \text{Me}$, **19**) led to decreased ee in the Mannich reaction (97% to 82% ee).

The effect of variations in the structure and stereochemistry of the diamine unit of the catalysts is summarized in Table 4. Incorporation of (*R,R*)-diphenylethylene diamine (**21**) was well tolerated in the Strecker reaction (98% ee), but was detrimental to the Mannich reaction (80% ee). Catalyst prepared from the sterically demanding (*R,R*)-di-*tert*-butyl-ethylene diamine (**22**) was inactive in both reactions. Incorporation of mismatched (*S,S*)-diamino-cyclohexane into catalyst (**23**) led to an unexpected result: while the Strecker reaction was catalyzed with precipitously lower enantioselectivity and a reversal in the sense of asymmetric induction relative to **1**, the Mannich reaction proceeded in 90% ee with the same sense of induction.

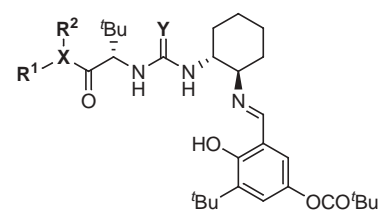
The remarkable indifference of the Mannich reaction to variations in the catalyst's salicylaldimine unit and diamine stereochemistry raised the compelling possibility that the entire diamine/Schiff base moiety might be excised from the catalyst structure without detrimental effect on enantioselectivity. To test this hypothesis, C_2 -symmetric catalyst **24** (Table 5) was prepared, incorporating all structural elements identified to be vital to stereoreduction within a symmetrical framework.¹⁴ However, catalyst **24** catalyzed the Mannich reaction of *N*-Boc benzaldimine with poor conversion and low enantioselectivity (42% ee).¹⁵ Returning to the original C_1 -symmetric design of **1**, catalyst **25**, wherein the diamine/Schiff base moiety was replaced with cyclohexylamine, was prepared and found to catalyze the Mannich reaction in 90% ee. Aniline derivative **26** afforded even higher levels of stereoreduction (94% ee and quantitative conversion within 48 h).¹⁶ Compound **26** represents a remarkable simplification in catalyst design, as it possesses less than half the molecular weight of parent catalyst **1** and two fewer stereocenters. It can be prepared readily from commercially available starting materials in 95% overall yield, with only a single chromatographic purification step.

While the Mannich and Strecker reactions are promoted with high ee using the same catalyst **1**, they in fact obey quite distinct stereoreduction profiles. This finding is perhaps not completely surprising given the nature of the imine substrates utilized in each reaction and fundamental differences in their respective nucleophiles. Nonetheless, it suggests that **1** might belong to the rapidly growing list of 'privileged' chiral catalysts: systems that promote high enantioselectivity in a range of mechanistically distinct reactions.¹⁷ Through mapping of the critical design features required for asymmetric induction, a new catalyst for the activation of *N*-Boc aldimines has been developed that possesses the minimal requirements for asymmetric induction. A catalyst derived from a single α -amino acid has been shown to impart enzyme-like enantioselectivity in a synthetically valuable transformation. Whereas proline and related secondary amine catalysts function as recyclable auxiliaries by covalently modifying either the nucleophile¹ or electrophile² to achieve high levels of asymmetric induction, C_1 -symmetric catalyst **26** induces high enantioselectivity through simple hydrogen-bonding interactions. The potential of small molecule hydrogen-bond donors in asymmetric catalysis appears to be quite significant,¹⁸ and is being explored aggressively in continuing studies.

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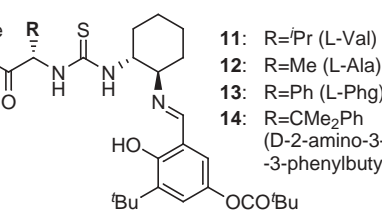


Scheme 1

Table 1 Modifications to the Amide Bond and Urea Moieties


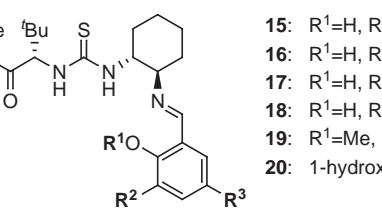
1: R¹=Bn, R²=Me, X=N, Y=S
 2: R¹=Bn, R²=H, X=N, Y=S
 3: R¹=Bn, R²=H, X=N, Y=O
 4: R¹=Bn, R²=Bn, X=N, Y=S
 5: R¹=Bn, R²=Bn, X=N, Y=O
 6: R¹=Me, R²=Me, X=N, Y=S
 7: R¹=Me, R²=Me, X=N, Y=O
 8: R¹=isobutyl, R²=isobutyl, X=N, Y=S
 9: R¹=ⁿHex, R²=H, X=N, Y=O
 10: R¹=Bn, X=O, Y=O

Catalyst	Strecker ee (%) ^a	Mannich ee (%) ^b	Catalyst	Strecker ee (%) ^a	Mannich ee (%) ^b
1	98	97 (97 ^c)	6	99	86
2	98	91	7	98	80
3	97	81	8	95	93
4	98	97	9	97	84
5	97	82	10	80	44

^a For experimental details on the Strecker reaction, see ref.^{5b}.^b For experimental details on the Mannich reaction, see ref.⁶.^c Reaction performed in THF.**Table 2** Variation of the Amino Acid


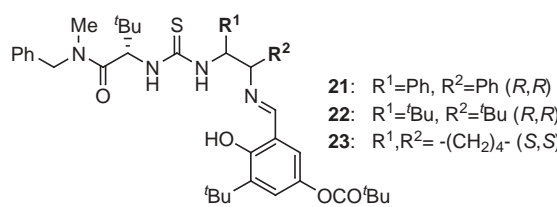
11: R=*i*Pr (L-Val)
 12: R=Me (L-Ala)
 13: R=Ph (L-Phg)
 14: R=CMe₂Ph (D-2-amino-3-methyl-3-phenylbutyric acid)

Catalyst	Strecker ee (%)	Mannich ee (%)	Catalyst	Strecker ee (%)	Mannich ee (%)
11	96	51	13	92	38
12	91	22	14^a	98 (R)	90 (S)

^a Enantiomeric catalyst prepared from D-amino acid and (S,S)-diaminocyclohexane.**Table 3** Salicylaldehyde Modifications


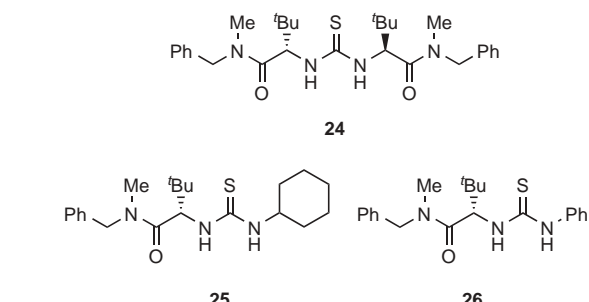
15: R¹=H, R²=*t*Bu, R³=*t*Bu
 16: R¹=H, R²=*i*Pr, R³=*t*Bu
 17: R¹=H, R²=Me, R³=*t*Bu
 18: R¹=H, R²=H, R³=H
 19: R¹=Me, R²=*t*Bu, R³=*t*Bu
 20: 1-hydroxy-2-naphthyl

Catalyst	Strecker ee (%)	Mannich ee (%)	Catalyst	Strecker ee (%)	Mannich ee (%)
15	92	97	18	94	91
16	92	97	19	64	82
17	91	96	20	67	94 (98 ^a)

^a Reaction performed in THF (see ref.¹³).**Table 4** Effects of Diamine Structure and Stereochemistry


21: R¹=Ph, R²=Ph (R,R)
 22: R¹=*t*Bu, R²=*t*Bu (R,R)
 23: R¹,R²=-(CH₂)₄- (S,S)

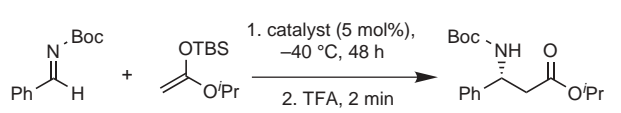
Catalyst	Strecker ee (%) ^a	Mannich ee (%) ^b
21	98	80
22	No reaction	No reaction
23	27 (R)	90

^a Strecker experimental procedure, see ref.⁶.^b Mannich experimental procedure, see ref.⁷.**Table 5** New Catalyst Designs for the Asymmetric Mannich Reaction


24

25

26



Catalyst	Conversion (%) ^a	ee (%)
24^b	37	42
25^b	90	90
26^c	100	94

^a Determined via GC relative to dodecane as an internal standard.^b Reaction performed in toluene.^c Reaction performed in THF.

Acknowledgment

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- (7) Kinetic studies carried out on both reactions are consistent with imine pre-association to catalyst followed by nucleophile addition to the catalyst-imine complex (ref.^{5c} and Wenzel, A. G., unpublished results).
- (8) The standard screening conditions are depicted in Scheme 1. Benzaldimines were chosen as substrates for each reaction to maximize structural and electronic similarity. While aliphatic *N*-alkyl imines have been successfully employed in the Strecker reaction, aliphatic *N*-Boc aldimines have not been investigated in the Mannich reaction because no useful method has been identified for their synthesis.
- (9) Although negligible improvement in the Strecker reaction was observed with the *N*-allyl benzaldimine substrate screened in this study, pronounced improvement has been observed in cases of problematic substrates. (See ref.^{5e})
- (10) In general, conversion was found to correlate with enantioselectivity, with the more selective catalysts also proving to be the most reactive.
- (11) For a comprehensive description of the effect of varying the R³ substituent on the enantioselectivity of the Strecker reaction, see ref.^{5a}
- (12) An optimization library performed during early-phase methodological development for the Mannich reaction revealed that variation of the R³ substituent of the salicylaldimine (R³ = *t*-Bu, Me, H, OTIPS, *t*-BuO, OMe, OCO-*t*-Bu, Br, Cl) has no effect on enantioselectivity or conversion (ref.⁶).
- (13) The Strecker reactions were carried out at lower catalyst loadings and more dilute conditions {[**20**] = 0.98 mM in the Strecker vs. 42 mM in the Mannich}, thereby obviating the need for a solvent switch with sparingly soluble **20**.
- (14) For discussions of the advantages of C₂-symmetry in asymmetric catalysts, see: (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Kagan, H. B. In *Comprehensive Asymmetric Catalysis*, Vol. 1; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, **1999**, Chap. 2.
- (15) Analogs of **24** derived from less sterically demanding amino acids (e.g. valine, alanine) also performed poorly as catalysts for the Mannich reaction. Catalyst **24** proved almost completely unreactive in the Strecker reaction.
- (16) The model Strecker reaction was catalyzed by **26** in 40% ee with the opposite sense of stereoinduction relative to **1**.
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