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De Novo Chiral Amino Alcohols in Catalyzing Asymmetric Additions to Aryl Aldehydes

Jian Huang,[†] James C. Ianni,[‡] Jennifer E. Antoline,[†] Richard P. Hsung,*[,†] and Marisa C. Kozlowski*[,‡]

Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705, and Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

rhsung@wisc.edu; marisa@sas.upenn.edu

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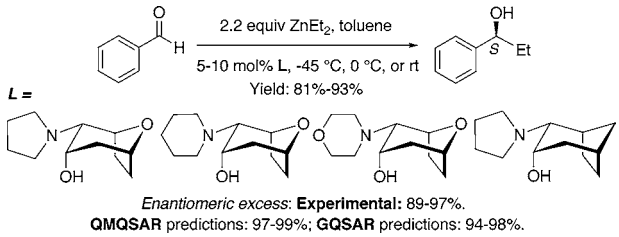
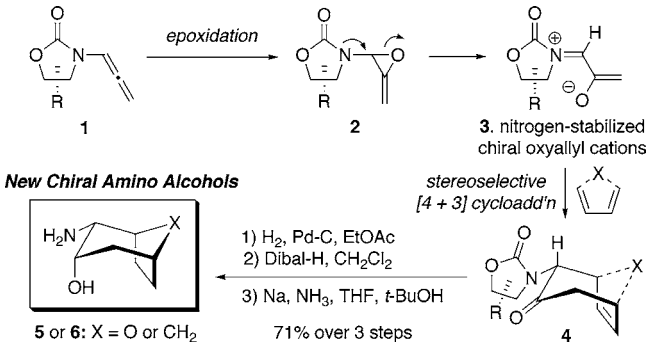
ABSTRACT



A de novo structural class of chiral amino alcohol catalysts has been identified through a synergistic effort combining novel architectures from [4 + 3] cycloadditions and quantum mechanical interaction field predictions that closely match subsequent experimental measurements.

We have been investigating a new class of chiral amino alcohols that could be prepared from chiral allenamides[1,2] and serve as ligands in asymmetric catalysis. Specifically, by employing chiral allenamides **1** as precursors to generate nitrogen-stabilized[3,4] chiral oxyallyl cations **3** via epoxidation (Scheme 1),[5] we were able to develop a highly stereoselective inter-[6] and intramolecular[7,8] (not shown) [4 + 3] cycloaddition[9] with dienes to give cycloadducts **4** and established an asymmetric 1,3-dipolar cycloaddition using Cu(II)−bisoxazoline catalysts.[10,11] Cycloadducts **4** embody a unique and structurally novel class of bicyclic α-amido ketone that

Scheme 1. Oxyallyl Cation [4 + 3] Cycloadditions



[†] University of Wisconsin.
[‡] University of Pennsylvania.

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can be transformed into chiral amino alcohols **5** and **6**.[6a] However, their capacity as chiral ligands is completely unprecedented.

Thus, given that we now have an efficient access to this class of substrates, we first assessed the ability of these new ligands as asymmetric catalysts in the alkylation of aryl aldehydes using a quantum mechanical QSAR analysis based on its excellent predictive potential.[12,13] Catalytic asymmetric additions to aldehydes and ketones represent an important venue in organic synthesis.[14−16] We report here our preliminary efforts unveiling these de novo chiral amino alcohols in asymmetric catalysis.

The enantiomeric excesses (ee) of the heretofore unknown β-amino alkoxide zinc catalysts (Figure 1) were predicted

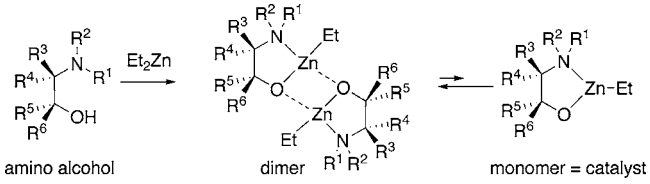

Figure 1. Asymmetric catalysis with chiral amino alcohols.

with 3D-QSSR (quantitative structural selectivity relationship) methods[17] employing quantum molecular interaction fields as implemented in the programs QMQSAR and GQSAR. Although detailed descriptions on how both these programs compute and utilize molecular fields are described elsewhere,[12,13] a short introduction is provided here. Two sets of catalysts are employed in generating predictions using this approach: a parametrization set to generate a model, and a prediction set to which this model is applied. For this asymmetric reaction, the parametrization set is composed of 18 β-amino alkoxide zinc catalysts that exhibit a wide range of enantioselection.[12b,18] This parametrization set was previously shown to provide internally consistent models,[12b,18] but the true test of the method lies in a priori predictions. For all the analyses, the enantioselectivities are converted to ΔG^{ee} using the relationship $\Delta G^{ee} = -RT\ln[(S)/(R)]$, so that the variables used in the correlation possess an underlying linear relationship.

For new chiral catalysts, prediction of enantioselectivities commences with calculation of the lowest energy catalyst conformers. For the benzaldehyde alkylation reaction, the dimeric catalyst structures (Figure 1) were found to provide the most robust models previously[18] and were subsequently employed in this analysis. Initially, conformers of the compounds were constructed and computed using the semiempirical method PM3 in Spartan.[19] These structures were used with the QMQSAR program. For the GQSAR program, the lowest energy conformers were subsequently geometry optimized using RHF/3-21G* and verified as ground-state minima by an additional frequency analysis.

All of the resultant dimers were then aligned about a set of common atoms. For QMQSAR, the alignment employed the Zn−O−N atoms. For GQSAR, the alignment employed the Zn−O−Zn−O atoms. A different alignment was utilized with QMQSAR since this program has a protocol to mask parts of the structure.

Both the QMQSAR and GQSAR programs employ quantum mechanical interaction fields in the form of electrostatic potential field (EPF) values computed at ordered grid points encompassing the compound. Either single-point PM3 semiempirical calculations with Divcon[20] (QMQSAR) or B3LYP/6-31G**[21] calculations with Gaussian03[22] (GQSAR) afforded the requisite electron densities employed in generating the EPF values for each compound along a common grid. Field spacing in the EPF was initially 0.35 Å and was adjusted during the course of the model building to a finer grid around correlated EPF points according to a MAXMIN diversity algorithm.[23] The EPF values represent the pool of independent variables from which the multi-linear regression (MLR) models were built.

Simple MLR models between the EPF points and the ΔG^{ee} values of the parametrization set were optimized by a

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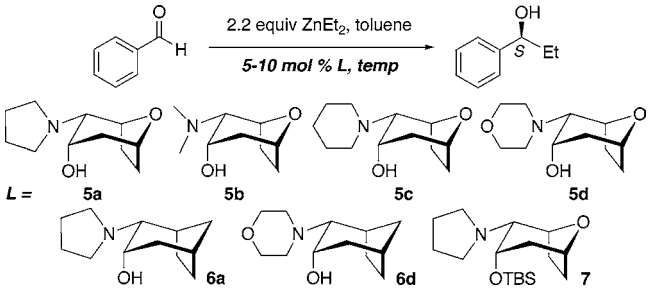
simulated Monte Carlo approach.[12] Overall, the minimal MLR models that provided highly cross-validated results of the parametrization set in the aldehyde alkylation were comprised of two EPF points per catalyst.[12b,18] In other words, two regions of the catalysts were found to account for most of the variance in ee; groups of different sizes or electronic aspects at these positions modify the enantioselection.

These models were subsequently used in generating predictions in the asymmetric alkylation of benzaldehyde for the six new amino alcohols **5a**−**d** and **6a** and **6d** (Scheme 2) incorporating the novel scaffold found in amines **5** and **6**.

Scheme 2. Chiral Amino Alcohols



For both QMQSAR and GQSAR, average ΔG predictions[12,18] (Table 1) were obtained from 18 separate models

Table 1. QMQSAR and GQSAR ΔG Predictions for Ligands **5a**−**d**, **6a**, and **6d**

	average predictions (18 models total)				
	QMQSAR		GQSAR		expt. values[a]
L	mean ΔG (kcal/mol)	SD (kcal/mol)	mean ΔG (kcal/mol)	SD (kcal/mol)	ΔG (kcal/mol)
5a	2.47	0.09	2.09	0.33	1.66
5b	2.37	0.15	2.06	0.26	
5c	2.51	0.11	2.08	0.26	1.80
5d	2.45	0.18	2.05	0.29	1.76
6a	2.39	0.08	2.03	0.22	1.83
6d	2.32	0.07	1.99	0.21	1.66

[a] Values obtained from ee results listed in Table 2 by using $\Delta G^{ee} = -RT\ln[(S)/(R)]$.

obtained with 17 parametrization compounds each. As indicated by the small standard deviations (SD) of the averaged results from these 18 models, it is clear that no single parametrization compound is providing an overwhelming bias. For convenience, the predicted energies are converted into enantioselectivities computed at the reaction temperatures employed, 228, 278, and 298 K (Table 2). The standard deviations (SD) from the average predictions also provide a measure of the error in the predictions, which is low for both the QMQSAR and GQSAR models. The enantioselectivity predictions for all six amino alcohols using both models are high. Prior work indicates that both the

Table 2. QMQSAR and GQSAR Enantioselectivity Predictions for Ligands **5a**−**d**, **6a**, and **6d**

	average predictions (18 Models Total)					
	QMQSAR		GQSAR		expt. values	
L	mean ee (%)	SD ee (%)	mean ee (%)	SD ee (%)	ee (%)	yield (%)
			228 K = −45 °C			
5a	99.2	0.1	98.1	0.7	95	81
5b	99.0	0.2	98.0	0.6		
5c	99.2	0.1	98.0	0.6	97	81
5d	99.1	0.2	97.9	0.7	97	81
6a	99.0	0.1	97.8	0.5		
6d	98.8	0.1	97.6	0.5	95	73
			278 K = 0 °C			
5a	98.0	0.2	95.9	1.2	90	90
5b	97.6	0.3	95.7	1.0		
5c	98.1	0.2	95.8	1.0	93	92
5d	97.9	0.4	95.6	1.1	91	90
6a	97.6	0.2	95.5	0.9	93	88
6d	97.3	0.2	95.1	0.9	79	86
			298 K = 25 °C			
5a	97.0	0.2	94.3	1.5	89	93
5b	96.5	0.4	94.1	1.3		
5c	97.2	0.3	94.3	1.2	89	87
5d	96.9	0.5	94.0	1.4	89	93
6a	96.6	0.2	93.8	1.1		
6d	96.1	0.2	93.3	1.1	44	53

QMQSAR and GQSAR models give highly predictive results, but that the GQSAR results exhibit slightly better correlations with experimental values.[13,18] On this basis, greater than 95% ee values were expected for the catalysts derived from **5a**, **5c**, **5d**, **6a**, or **6d** in the asymmetric alkylation of benzaldehyde at −45 °C (see Scheme 2).

Encouraged by these predictions, we prepared the derivatives illustrated in Scheme 2 from [4 + 3] adduct **4** (Scheme 1) and examined these compounds in this transformation.[24] Reactions were performed in toluene at various temperatures using 2.2 equiv of Et_2Zn and 5−10 mol % of the respective ligands, **5a**, **5c**, **5d**, **6a**, or **6d**.[25] Gratifyingly, all the additions were achieved in high yields (Table 2), indicating that these new chiral amino alcohols form highly active catalysts. More significantly, ≥90% ee was obtained experimentally in almost all cases, closely matching the QMQSAR and GQSAR predictions (Tables 1 and 2). Reasons for lower but reproducible ee values obtained using **6d** at 0 °C and room temperature are not clear at this point; however, the 95% ee observed at −45 °C indicates that the results at higher temperature reflect a secondary effect rather than the inherent enantioselection. The difference in ee between 5 and 10 mol % ligand is negligible, indicating little competition from other less selective pathways. In line with prior results, QMQSAR

(24) See Supporting Information. Due to low yields in the preparation and purification, **5b** was not examined. We appreciate one reviewer's suggestion of White's protocol as a viable option: White, J. D.; Wardrop, D. J.; Sunderman, K. F. *Org. Synth.* **2002**, *79*, 125 and 130.

(25) Enantiomeric excess values were determined using HPLC with a Chiralcel-OD column at 254 nm.

tends to overpredict the enantioselectivity with a range of 97−99% ee, whereas GQSAR predictions with a range of 94−98% ee are closer to the actual experimental values (Table 2).

On the basis of the assignment of absolute configuration of the resulting alcohol, a model using ligand **5a** is proposed in Figure 2. The regions in red outline the portions of the

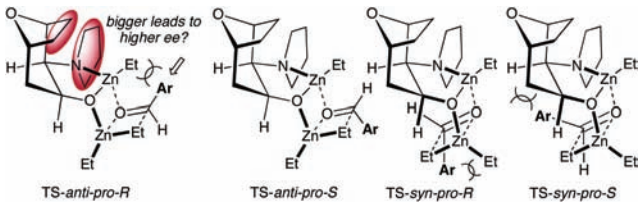


Figure 2. Proposed stereochemical models.

catalyst that the QSSR models identified as important to enantioselection; in general, moderate steric bulk at these positions increases ee. The model reveals interesting structural features of this new catalytic system. The unique oxabicyclic scaffold of **5a** provides an inflexible backbone suitable for rigid complexation with Zn. Such rigidity allows for an excellent transfer of the chiral information from the indicated ligand substituents to the transition state (TS) maximizing the energetic difference between *pro-R* and *pro-S* transition states and leading to high enantioselectivities.

Of the four canonical transition states, *anti-pro-R/S* and *syn-pro-R/S*,[26] the two *anti* transition states are more favorable due to the large bulk of the chiral ligand that compresses the *syn* transition states leading to disfavorable steric interactions. Among the *anti* transition states, a more severe steric interaction between Ar and Et groups in TS-*anti-pro-R* results in greater stability for TS-*anti-pro-S*, which accounts for the observed *S*-enantiomer.

This proposed model is consistent with several additional experiments. First, disruption of coordination to the zinc by silylation of the alcohol oxygen atom in **5a** as in **7** (Scheme 2) clearly diminished the ability of the ligand to provide asymmetric induction in the addition to benzaldehyde (90% yield, 88% ee vs 65% yield, 0% ee). Second, the above models indicate that large aldehyde substituents amplify the steric repulsion in TS-*anti-pro-R* and lead to higher ee. In accord with this observation, the ee increased as the size of

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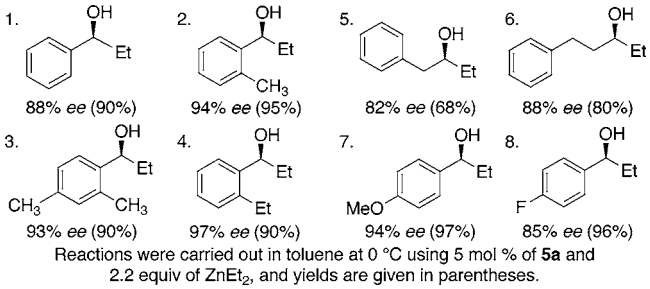

Figure 3. Results with additional substrates and **5a**.

the aryl group of the aldehyde increased (Figure 3, entry 1 vs entries 2−4).

Along the same line, when the size decreased from Ph to Bn, the ee decreased noticeably (entry 1 vs entry 5). Intriguingly, the ee did not suffer any further loss and actually increased slightly with an additional methylene unit as shown in entry 6. This finding also implies that these new ligands can be useful in asymmetric additions to simple alkyl aldehydes (entries 5 and 6), which remain a challenge in the field.

Finally, the result in entry 7 suggests that a more electron-rich and Lewis basic aldehyde carbonyl oxygen (*para*-methoxybenzaldehyde) with tighter coordination to Zn further enhances the difference between TS-*anti-pro-R* and TS-*anti-pro-S* and leads to higher ee. Thus, a less electron-rich and Lewis basic carbonyl oxygen, as in *para*-fluorobenzaldehyde, should provide lower ee, as was seen in entry 8. It should be noted here that, although not shown, enantiomers of these new chiral amino alcohols could be prepared from either diastereoselective or enantioselective [4 + 3] cycloadditions and, thus, in principle, utilized to provide the antipodes (*R*-enantiomers) of the addition products.

Herein, we have described the identification of a class of structurally novel chiral amino alcohols for use in asymmetric catalysis through an approach that utilizes simple, rapid, and highly predictive 3D-QSSR analyses.

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Supporting Information Available: Experimental details, NMR spectra for all new compounds, and the full citation of reference 22. This material is available free of charge via the Internet at http://pubs.acs.org.

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